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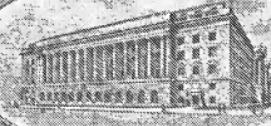
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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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MAIL STOP PROVISIONAL APPLICATION  
 Commissioner for Patents  
 P.O. Box 1450  
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PROVISIONAL APPLICATION COVER SHEET

Sir:

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under  
 37 CFR 1.53(c).

Docket Number				CL001491-P1
INVENTOR(s) / APPLICANT(s)				
Last Name	First Name	Middle Name	RESIDENCE (City and either State or Foreign Country)	
LINK	JOHN	O.	SAN FRANCISCO, CA 94110 - U.S.A.	
TITLE OF THE INVENTION				
SILINANE COMPOUNDS AS CYSTEINE PROTEASE INHIBITORS				
CORRESPONDENCE ADDRESS				
Customer Number or Bar Code Label		23519	or Correspondence address below (Insert Customer No. or Attach bar code label here)	
ENCLOSED APPLICATION PARTS (check all that apply)				
67 Pages Specification		<input checked="" type="checkbox"/> Other (specify)		
14 Pages Claims (Optional)		Postcard		
1 Page Abstract (Optional)		Certificate of Mailing Title Sheet		
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METHOD OF PAYMENT (check one)				
<input type="checkbox"/> A check is enclosed to cover the Provisional Filing Fee <input checked="" type="checkbox"/> <b>The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 50-0970</b>				PROVISIONAL FILING FEE AMOUNT (\$)
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Was the invention made by an agency of the United States Government or under a contract with an agency of the United States Government?

No.

Yes, the name of the U.S. Government agency and the Government contract number are: \_\_\_\_\_

The above FEE is believed to be correct. However, the Commissioner is authorized to charge any deficiencies or credit any overpayments to Deposit Account No. 50-0970.

Respectfully submitted,

Rekha Bansal, Reg. No. 36,440

Date: February 24, 2004

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By: Debra K. Bowen Date: Feb. 24, 2004  
Debra K. Bowen

#### SILINANE COMPOUNDS AS CYSTEINE PROTEASE INHIBITORS

##### **Inventor**

John O. Link

## SILINANE COMPOUNDS AS CYSTEINE PROTEASE INHIBITORS

### Field of the Invention

The present invention is directed to compounds that are inhibitors of cysteine proteases, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is directed to pharmaceutical compositions comprising these compounds and processes for preparing them. The present invention is also directed to the use of these inhibitors in combination with a therapy that causes a deleterious immune response in patients receiving the therapy.

10

### State of the Art

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increased expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy, and others. For example, increased cathepsin B levels and redistribution of the enzyme are found in tumors; thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

The prominent expression of cathepsin K in osteoclasts and osteoclast-related multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in ososteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest that the enzyme plays a role in pulmonary disorders as well.

Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis. In addition, cathepsin S is

implicated in allergic disorders, including, but not limited to asthma; and allogeneic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts.

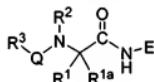
Another cysteine protease, Cathepsin F, has been found in macrophages and is involved in antigen processing. It is believed that Cathepsin F in stimulated lung macrophages and possibly

5 other antigen presenting cells could play a role in airway inflammation (see G. P. Shi et al, *J. Exp. Med.* 2000, 191,1177)

In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules which inhibit the activity of this class of enzymes, in particular molecules which inhibit 10 cathepsins B, K, L, F, and/or S, will therefore be useful as therapeutic agents.

#### DETAILED DESCRIPTION

In a first aspect, this invention is directed to a method for treating a disease in an animal mediated by cysteine proteases, in particular cathepsin S, which method comprises administering 15 to the animal a therapeutically effective amount of a compound of Formula (I):



(I)

where:

Q is  $-\text{CO}-$ ,  $-\text{SO}_2-$ ,  $-\text{OCO}-$ ,  $-\text{NR}^4\text{CO}-$ ,  $-\text{NR}^4\text{SO}_2-$ , or  $-\text{CHR}-$  where R is haloalkyl and  $\text{R}^4$  is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or aralkyl;

20 E is:

(i)  $-\text{C}(\text{R}^5)(\text{R}^6)\text{X}^1$  where  $\text{X}^1$  is  $-\text{CHO}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CF}_3$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CF}_2\text{CF}_2\text{R}^9$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{R}^{10}$ ,  $-\text{CH}=\text{CHS}(\text{O})_2\text{R}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{R}^7)(\text{R}^8)\text{OR}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CH}_2\text{OR}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{R}^7)(\text{R}^8)\text{R}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CH}_2\text{N}(\text{R}^{11})\text{SO}_2\text{R}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CF}_2\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^{11})(\text{CH}_2)_2\text{OR}^{11}$ , or

25  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^{11})(\text{CH}_2)_2\text{NR}^{10}\text{R}^{11}$ ; or

(ii)  $-\text{C}(\text{R}^{5\text{a}})(\text{R}^{6\text{a}})\text{CN}$ ;

where:

$\text{R}^5$  and  $\text{R}^{5\text{a}}$  are independently hydrogen or alkyl; and

R<sup>6</sup> and R<sup>6a</sup> are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, -alkylene-X<sup>2</sup>-R<sup>12</sup> (where X<sup>2</sup> is -O-, -NR<sup>13</sup>-, -S(O)<sub>n1</sub>-, -CONR<sup>13</sup>-, -NR<sup>13</sup>CO-, -NR<sup>13</sup>C(O)O-, -NR<sup>13</sup>CONR<sup>13</sup>-, -OCONR<sup>13</sup>-, -NR<sup>13</sup>SO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>13</sup>-, -NR<sup>13</sup>SO<sub>2</sub>NR<sup>13</sup>-, -CO-, or -

5 OCO- where n1 is 0-2 and each R<sup>13</sup> is hydrogen or alkyl) and R<sup>12</sup> hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl wherein the aromatic or alicyclic ring in R<sup>6</sup> and R<sup>6a</sup> is optionally substituted with one, two, or three R<sup>8</sup> independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, nitro, aryloxy, 10 benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl where the aromatic or alicyclic ring in R<sup>8</sup> is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl; or

15 R<sup>5</sup> and R<sup>6</sup> and R<sup>5a</sup> and R<sup>6a</sup> taken together with the carbon atom to which both R<sup>5</sup> and R<sup>6</sup> and R<sup>5a</sup> and R<sup>6a</sup> are attached form (i) cycloalkylene optionally substituted with one or two R<sup>b</sup> independently selected from alkyl, halo, alkylamino, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxy carbonyl, or (ii) heterocycloalkylene optionally substituted with one to four alkyl or one or two R<sup>c</sup> independently selected from alkyl, haloalkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, 20 aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -S(O)<sub>n2</sub>R<sup>14</sup>, -alkylene-S(O)<sub>n2</sub>-R<sup>15</sup>, -COOR<sup>16</sup>, -alkylene-COOR<sup>17</sup>, -CONHR<sup>18</sup>R<sup>19</sup>, or -alkylene-CONHR<sup>20</sup>R<sup>21</sup> (where n2 is 0-2 and R<sup>14</sup>-R<sup>17</sup>, R<sup>18</sup> and R<sup>20</sup> are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and R<sup>19</sup> and R<sup>21</sup> are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to cycloalkylene or heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, or acyl;

25 R<sup>7</sup> is hydrogen or alkyl;

30 R<sup>8</sup> is hydroxy; or

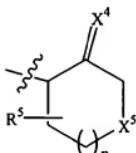
R<sup>7</sup> and R<sup>8</sup> together form oxo;

R<sup>9</sup> is hydrogen, halo, alkyl, aralkyl or heteroaralkyl;

$R^{10}$  is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in  $R^{10}$  is optionally substituted with one, two, or three  $R^d$  independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, carbamoyl, or acyl and wherein the aromatic or alicyclic ring in  $R^d$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino; and

10  $R^{11}$  is hydrogen or alkyl; or

(iii) a group of formula (a):



(a)

15 where:

$n$  is 0, 1, or 2;

$X^4$  is selected from  $-NR^{22}$ ,  $-S-$ , or  $-O-$  where  $R^{22}$  is hydrogen, alkyl, or alkoxy; and

$X^5$  is  $-O-$ ,  $-S-$ ,  $-SO_2-$ , or  $-NR^{23}$  where  $R^{23}$  is selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,  $-S(O)_2R^{24}$ ,  $-alkylene-S(O)_{n3}-R^{25}$ ,  $-COOR^{26}$ ,  $-alkylene-COOR^{27}$ ,  $-CONR^{28}R^{29}$ , or  $-alkylene-CONR^{30}R^{31}$  (where  $n3$  is 0-2 and  $R^{24}$ - $R^{27}$ ,  $R^{28}$  and  $R^{30}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl and  $R^{29}$  and  $R^{31}$  are independently hydrogen or alkyl) where the aromatic or alicyclic ring in  $R^{23}$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl and one substituent selected from aryl, aralkyl, heteroaryl, or heteroaralkyl; and

20  $R^5$  is as defined above;

25

R<sup>1</sup> is hydrogen or alkyl;

R<sup>1a</sup> is 1,1-dialkylsilinan-4-ylalkylene or -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl, R<sup>33</sup> is alkyl, and R<sup>34</sup> is alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, or heterocycloalkylalkyl or R<sup>33</sup> and R<sup>34</sup> together with Si form a heterocycloalkylene ring containing a

5 Si atom and 3 to 7 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with -NH-, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CONH-, or -SO<sub>2</sub>NH- and wherein the aralkyl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylene ring in R<sup>1a</sup> is optionally substituted on the ring with one, two, or three R<sup>e</sup> independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted 10 amino, disubstituted amino, nitro, aryloxy, benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl and further wherein the aromatic or alicyclic ring in R<sup>e</sup> is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl;

R<sup>2</sup> is hydrogen or alkyl;

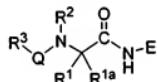
15 R<sup>3</sup> is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, or -alkylene-X<sup>6</sup>-R<sup>35</sup> [wherein X<sup>6</sup> is -NR<sup>36</sup>-, -O-, -S(O)n4-, -CO-, -COO-, -OCO-, -NR<sup>36</sup>CO-, -CONR<sup>36</sup>-, -NR<sup>36</sup>SO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>36</sup>-, -NR<sup>36</sup>COO-, -OCONR<sup>36</sup>-, -NR<sup>36</sup>CONR<sup>37</sup>-, or -NR<sup>36</sup>SO<sub>2</sub>NR<sup>37</sup>- (where each R<sup>36</sup> and R<sup>37</sup> are independently hydrogen, alkyl, or acyl and n4 is 0-2) and R<sup>35</sup> is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, 20 heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the alkylene chain in R<sup>3</sup> is optionally substituted with one to four halo atoms and the aromatic and alicyclic rings in R<sup>3</sup> are optionally substituted by one, two, or three R<sup>f</sup> independently selected from alkyl, aminoalkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, 25 heterocycloalkylalkyl, aryloxy, benzyloxy, carboxy, alkoxy carbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkyl carbamoyloxy, aryl carbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, aralkylaminosulfonyl, aminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, amino, 30 monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in R<sup>f</sup> are optionally substituted with one, two, or three R<sup>g</sup> wherein R<sup>g</sup> is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl,

aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxy carbonyl; or a pharmaceutically acceptable salts thereof.

Preferably, the disease is juvenile onset diabetes, psoriasis, multiple sclerosis, pemphigus

5 vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis, allergic disorders, including, but not limited to, asthma, allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts and endometriosis, chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonitis and cardiovascular disease such as  
10 plaque rupture and atherosclerosis, systemic amyloidosis, Alzheimer's disease, and iatrogenic disorders. Preferably, psoriasis, iatrogenic disorders, and myasthenia gravis.

In a second aspect, this invention is directed to a compound of Formula (I):



(I)

wherein:

15 Q is  $-\text{CO}-$ ,  $-\text{SO}_2-$ ,  $-\text{OCO}-$ ,  $-\text{NR}^4\text{CO}-$ ,  $-\text{NR}^4\text{SO}_2-$ , or  $-\text{CHR}-$  where R is haloalkyl and  $\text{R}^4$  is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or aralkyl;

E is:

(i)  $-\text{C}(\text{R}^5)(\text{R}^6)\text{X}^1$  where  $\text{X}^1$  is  $-\text{C}(\text{R}^7)(\text{R}^8)\text{R}^{10}$ ,  $-\text{CH}=\text{CHS}(\text{O})_2\text{R}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{R}^7)(\text{R}^8)\text{OR}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CH}_2\text{OR}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CH}_2\text{N}(\text{R}^{11})\text{SO}_2\text{R}^{10}$ ,  
20  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^{11})(\text{CH}_2)_2\text{QR}^{11}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$  or  
 $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^{11})(\text{CH}_2)_2\text{NR}^{10}\text{R}^{11}$ ; or  
(ii)  $-\text{C}(\text{R}^{5a})(\text{R}^{6a})\text{CN}$ ;

where:

$\text{R}^5$  and  $\text{R}^{5a}$  are independently hydrogen or alkyl; and

25  $\text{R}^6$  and  $\text{R}^{6a}$  are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl,  $-\text{alkylene-X}^2\text{R}^{12}$  (where  $\text{X}^2$  is  $-\text{O}-$ ,  $-\text{NR}^{13}-$ ,  $-\text{S}(\text{O})_{\text{n}1}\text{R}-$ ,  $-\text{CONR}^{13}-$ ,  $-\text{NR}^{13}\text{CO}-$ ,  $-\text{NR}^{13}\text{C}(\text{O})\text{O}-$ ,  $-\text{NR}^{13}\text{CONR}^{13}-$ ,  $-\text{OCONR}^{13}-$ ,  $-\text{NR}^{13}\text{SO}_2-$ ,  $-\text{SO}_2\text{NR}^{13}-$ ,  $-\text{NR}^{13}\text{SO}_2\text{NR}^{13}-$ ,  $-\text{CO}-$ , or  $-\text{OCO}-$  where  $\text{n}1$  is 0-2 and each  $\text{R}^{13}$  is hydrogen or alkyl) and  $\text{R}^{12}$  hydrogen, alkyl, haloalkyl,

cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl wherein the aromatic or alicyclic ring in  $R^6$  and  $R^{6a}$  is optionally substituted with one, two, or three  $R^8$  independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monosubstituted amino, disubstituted amino, nitro, aryloxy, or benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl where the aromatic or alicyclic ring in  $R^8$  is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl; or

5       $R^5$  and  $R^6$  and  $R^{5a}$  and  $R^{6a}$  taken together with the carbon atom to which both  $R^5$  and  $R^6$  and  $R^{5a}$  and  $R^{6a}$  are attached form (i) cycloalkylene optionally substituted with one or two  $R^b$  independently selected from alkyl, halo, alkylamino, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxycarbonyl, or aryloxy carbonyl, or (ii) heterocycloalkylene optionally substituted with one to four alkyl or one or two  $R^c$  independently selected from alkyl, haloalkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, or

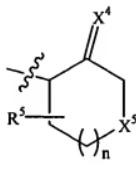
10     15     20     25     30     aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl,  $-S(O)_{n2}R^{14}$ ,  $-alkylene-S(O)_{n2}R^{15}$ ,  $-COOR^{16}$ ,  $-alkylene-COOR^{17}$ ,  $-CONHR^{18}R^{19}$ , or  $-alkylene-CONHR^{20}R^{21}$  (where  $n2$  is 0-2 and  $R^{14}$ - $R^{17}$ ,  $R^{18}$  and  $R^{20}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and  $R^{19}$  and  $R^{21}$  are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to cycloalkylene or heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monosubstituted amino, disubstituted amino, or acyl;  $R^7$  is hydrogen or alkyl;  $R^8$  is hydroxy; or  $R^7$  and  $R^8$  together form oxo;  $R^{10}$  is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in  $R^{10}$  is optionally substituted with one, two, or three  $R^d$  independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryl, aralkyl, heteroaryl, amino, monosubstituted amino, disubstituted amino, carbamoyl, or acyl and wherein the aromatic or

alicyclic ring in  $R^d$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino; and

$R^{11}$  is hydrogen or alkyl provided that when  $E$  is  $-C(R^7)(R^8)C(O)NR^{10}R^{11}$  then  $R^{11}$  is alkyl;

5 or

(iii) a group of formula (a):



(a)

10 where:

$n$  is 0, 1, or 2;

$X^4$  is selected from  $-NR^{22}-$ ,  $-S-$ , or  $-O-$  where  $R^{22}$  is hydrogen, alkyl, or alkoxy; and

$X^5$  is  $-O-$ ,  $-S-$ ,  $-SO_2-$ , or  $-NR^{23}-$  where  $R^{23}$  is selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl,

15 heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,  $-S(O)_2R^{24}$ ,  $-alkylene-S(O)_{n3}R^{25}$ ,  $-COOR^{26}$ ,  $-alkylene-COOR^{27}$ ,  $-CONR^{28}R^{29}$ , or  $-alkylene-CONR^{30}R^{31}$  (where  $n3$  is 0-2 and  $R^{24}$ - $R^{27}$ ,  $R^{28}$  and  $R^{30}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl and  $R^{29}$  and  $R^{31}$  are independently hydrogen or alkyl) where the aromatic or alicyclic ring in  $R^{23}$  is optionally

20 substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl and one substituent selected from aryl, aralkyl, heteroaryl, or heteroaralkyl; and

$R^5$  is as defined above;

$R^1$  is hydrogen or alkyl;

25  $R^{1a}$  is 1,1-dialkylsilyl and 4-ylalkylene or  $-(alkylene)-SiR^{32}R^{33}R^{34}$  where  $R^{32}$  is alkyl,  $R^{33}$  is alkyl, and  $R^{34}$  is alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, or heterocycloalkylalkyl or  $R^{33}$  and  $R^{34}$  together with Si form a heterocycloalkylene ring containing a Si atom and 3 to 7 carbon ring atoms wherein one or two carbon ring atoms are optionally

independently replaced with -NH-, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CONH-, or -SO<sub>2</sub>NH- and  
wherein the aralkyl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylene ring in R<sup>1a</sup> is  
optionally substituted on the ring with one, two, or three R<sup>e</sup> independently selected from alkyl,  
haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted  
5 amino, disubstituted amino, nitro, aryloxy, benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl and  
further wherein the aromatic or alicyclic ring in R<sup>e</sup> is optionally substituted with one or two  
substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy,  
amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl;

R<sup>2</sup> is hydrogen or alkyl;

10 R<sup>3</sup> is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,  
heterocycloalkyl, heterocycloalkylalkyl, or -alkylene-X<sup>6</sup>-R<sup>35</sup> [wherein X<sup>6</sup> is -NR<sup>36</sup>-, -O-, -S(O)n<sup>4</sup>-,  
-CO-, -COO-, -OCO-, -NR<sup>36</sup>CO-, -CONR<sup>36</sup>-, -NR<sup>36</sup>SO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>36</sup>-, -NR<sup>36</sup>COO-, -OCONR<sup>36</sup>-, -  
NR<sup>36</sup>CONR<sup>37</sup>-, or -NR<sup>36</sup>SO<sub>2</sub>NR<sup>37</sup>- (where each R<sup>36</sup> and R<sup>37</sup> are independently hydrogen, alkyl, or  
acyl and n<sup>4</sup> is 0-2) and R<sup>35</sup> is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl,

15 heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the  
alkylene chain in R<sup>3</sup> is optionally substituted with one to four halo atoms and the aromatic and  
alicyclic rings in R<sup>3</sup> are optionally substituted by one, two, or three R<sup>f</sup> independently selected from  
alkyl, aminoalkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy,  
aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,

20 heterocycloalkylalkyl, aryloxy, benzyloxy, carboxy, alkoxy carbonyl, aryloxy carbonyl, carbamoyl,  
alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxy carbonyl amino,  
aryloxy carbonyl amino, alkyl carbamoyloxy, aryl carbamoyloxy, alkylsulfonyl amino,  
arylsulfonyl amino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl,  
aralkylaminosulfonyl, amino carbonyl, arylaminocarbonyl, aralkylaminocarbonyl, amino,  
25 monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in R<sup>f</sup>  
are optionally substituted with one, two, or three R<sup>g</sup> wherein R<sup>g</sup> is independently selected from  
alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl,  
aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl,  
heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxy carbonyl; or  
30 a pharmaceutically acceptable salts thereof.

In a third aspect this invention is directed to a pharmaceutical composition comprising a  
compound of Formula (I) or a pharmaceutically acceptable salt thereof, in admixture with a

suitable excipient.

In a fourth aspect this invention is directed to a method of treating a patient undergoing a therapy wherein the therapy causes an immune response in the patient comprising administering to the patient a compound of Formula (I) or a pharmaceutically acceptable salt thereof. Preferably,

5 the immune response is mediated by MHC class II molecules. The compound of this invention can be administered prior to, simultaneously, or after the therapy. Preferably, the therapy involves treatment with a biologic. Preferably, the therapy involves treatment with a small molecule.

Preferably, the biologic is a protein or an antibody, preferably a monoclonal antibody.

More preferably, the biologic is Remicade®, Refacto®, Referon-A®, Factor VIII, Factor VII, 10 Betaseron®, Epogen®, Embrel®, Interferon beta, Botox®, Fabrazyme®, Elspar®, Cerezyme®, Myobloc®, Aldurazyme®, Verluma®, Interferon alpha, Humira®, Aranesp®, Zevalin® or OKT3.

Preferably, the treatment involves use of heparin, low molecular weight heparin, procainamide or hydralazine.

In a fifth aspect, this invention is directed to a method of treating immune response in an 15 animal that is caused by administration of a biologic to the animal which method comprises administering to the animal in need of such treatment a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In a sixth aspect, this invention is directed to a method of conducting a clinical trial for a biologic comprising administering to an individual participating in the clinical trial a compound of 20 Formula (I) or a pharmaceutically acceptable salt thereof with the biologic.

In a seventh aspect, this invention is directed to a method of prophylactically treating a person undergoing treatment with a biologic with a compound of Formula (I) or a pharmaceutically acceptable salt thereof to treat the immune response caused by the biologic in the person.

25 In an eighth aspect, this invention is directed to a method of determining the loss in the efficacy of a biologic in an animal due to the immune response caused by the biologic comprising administering the biologic to the animal in the presence and absence of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In a ninth aspect, this invention is directed to a method of improving efficacy of a biologic 30 in an animal comprising administering the biologic to the animal with a compound of of Formula (I) or a pharmaceutically acceptable salt thereof.

In a tenth aspect, this invention is directed to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

In a eleventh aspect, this invention is directed to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for combination

5 therapy with a biologic, wherein the compound of this invention treats the immune response caused by the biologic.

Preferably, the Cathepsin S inhibitor is administered prior to the administration of the biological agent.

10 Preferably, the Cathepsin S inhibitor is administered concomitantly with the biological agent.

Preferably, the Cathepsin S inhibitor is administered after the administration of the biological agent.

#### DETAILED DESCRIPTION OF THE INVENTION

##### 15 Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

"Alicyclic" means cycloalkyl and heterocycloalkyl rings as defined herein.

20 "Alkyl" represented by itself means a straight or branched, saturated aliphatic radical containing one to six carbon atoms, unless otherwise indicated (e.g., alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, and the like).

"Alkenyl" represented by itself means a straight or branched, aliphatic radical of two to six carbon atoms containing one or two double bond e.g., ethyneyl, propenyl, and the like.

25 "Alkylene", unless indicated otherwise, means a straight or branched, saturated aliphatic, divalent radical having the number of one to six carbon atoms, e.g., methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), trimethylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), tetramethylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-) 2-methyltetramethylene (-CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-), pentamethylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), and the like.

30 "Alkylcarbamoyloxy" refers to a radical -OCONHR where R is an alkyl group e.g., methylcarbamoyloxy, ethylcarbamoyloxy, and the like.

"Alkylsulfonylamino" refers to a radical -NHSO<sub>2</sub>R where R is an alkyl group e.g., methylsulfonylamino, ethylsulfonylamino, and the like.

"Amino" means the radical -NH<sub>2</sub>.

"Aminosulfonyl" refers to a radical -SO<sub>2</sub>NH<sub>2</sub>.

"Alkylaminosulfonyl" or "dialkylaminosulfonyl" refers to a radical -SO<sub>2</sub>NHR and -SO<sub>2</sub>NRR' respectively, where R and R' are independently alkyl group e.g., methylaminosulfonyl, 5 and the like.

"Alkylamino" or "dialkylamino" refers to a radical -NHR and -NRR' respectively, where R and R' are independently alkyl group e.g., methylamino, dimethylamino, and the like.

"Alkoxy" refers to a radical -OR where R is an alkyl group e.g., methoxy, ethoxy, and the like.

10 "Alkoxy carbonyl" refers to a radical -C(O)OR where R is an alkyl group e.g., methoxycarbonyl, ethoxycarbonyl, and the like.

"Alkoxy carbonylalkyl" means the radical -(alkylene)-C(O)OR where R is alkyl as defined above e.g., methoxycarbonylalkyl, 2-, or 3-ethoxycarbonylmethyl, and the like.

15 "Alkoxy carbonyl amino" refers to a radical -NHC(O)OR where R is an alkyl group e.g., methoxycarbonyl amino, ethoxycarbonyl amino, and the like.

"Alkoxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one alkoxy group, preferably one or two alkoxy groups, as defined above, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like.

20 "Alkoxyalkyloxyalkyl" refers to a radical -(alkylene)-O-(alkylene)-OR where R is an alkyl group e.g., as defined above, e.g., 2-methoxyethoxyethyl, 3-methoxypropoxyethyl, and the like.

"Aminoalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with at least one, 25 preferably one or two, -NRR' where R is hydrogen, alkyl, or -COR<sup>a</sup> where R<sup>a</sup> is alkyl, and R' is hydrogen or alkyl, e.g., aminomethyl, methylaminoethyl, dimethylaminoethyl, 1,3-diaminopropyl, acetylaminopropyl, and the like.

"Alkylthio" refers to a radical -SR where R is an alkyl group e.g., methylthio, ethylthio, and the like.

30 "Alkylsulfinyl" refers to a radical -S(O)R where R is an alkyl group e.g., methylsulfinyl, ethylsulfinyl, and the like.

"Alkylsulfonyl" refers to a radical  $-SO_2R$  where R is an alkyl group e.g., methylsulfonyl, ethylsulfonyl, and the like.

"Acyl" means a radical  $-COR$  where R is hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkyl as defined herein, e.g., formyl, acetyl,

5 trifluoroacetyl, benzoyl, piperazin-1-ylcarbonyl, and the like.

"Acyloxy" means a radical  $-OCOR$  where R is alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or heterocycloalkyl as defined herein, e.g., acetoxy, trifluoroacetoxy, benzoyloxy, piperazin-1-ylcarbonyloxy, and the like.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

10 "Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are  $sp^2$  hybridized and the total number of pi electrons is equal to  $4n+2$ .

"Aryl" means a monocyclic or fused bicyclic ring assembly containing 6 to 10 ring carbon atoms unless otherwise indicated, wherein each ring is aromatic e.g., phenyl or anthryl.

15 "Aralkyl" means a radical  $-(alkylene)-R$  where R is aryl as defined above e.g., benzyl, phenethyl, and the like.

"Aryloxy" means a radical  $-OR$  where R is aryl as defined above.

"Aryloxyalkyl" means the radical  $-(alkylene)-OR$  where R is aryl as defined above e.g.,

20 phenoxymethyl, 2-, or 3-phenoxymethyl, and the like.

"Aryloxycarbonyl" means the radical  $-C(O)OR$  where R is aryl as defined above e.g., phenyloxycarbonyl, and the like.

"Arylcaramoyloxy" means the radical  $-OC(O)NHR$  where R is aryl as defined above e.g., phenylcarbamoyloxy, and the like.

25 "Arylthio" refers to a radical  $-SR$  where R is an aryl group e.g., phenylthio, and the like.

"Arylsulfinyl" refers to a radical  $-SOR$  where R is an aryl group e.g., phenylsulfinyl, and the like.

"Arylsulfonyl" refers to a radical  $-SO_2R$  where R is an aryl group e.g., phenylsulfonyl, and the like.

30 "Aryloxycarbonylamino" refers to a radical  $-NHC(O)OR$  where R is an aryl group e.g., phenoxy carbonylamino, and the like.

"Arylsulfonylamino" refers to a radical  $-NHSO_2R$  where R is an aryl group as defined above, unless otherwise stated e.g., phenylsulfonylamino, and the like.

"Arylaminosulfonyl" means the radical  $-SO_2NHR$  where R is aryl as defined above e.g., phenylaminosulfonyl, and the like.

5 "Aralkylaminosulfonyl" means the radical  $-SO_2NHR$  where R is aralkyl as defined above e.g., benzylaminosulfonyl, and the like.

"Arylaminocarbonyl" means the radical  $-CONHR$  where R is aryl as defined above e.g., phenylaminosulfonylcarbonyl, and the like.

10 "Aralkylamino $\bar{c}$ arbonyl" means the radical  $-CONHR$  where R is aralkyl as defined above e.g., benzylaminocarbonyl, and the like.

"Biologic" means a therapeutic agent originally derived from living organisms for the treatment or management of a disease. Examples include, but are not limited to, proteins (recombinant and plasma derived), monoclonal or polyclonal, humanized or murine antibodies, toxins, hormones, and the like. Biologics are currently available for the treatment of a variety of 15 diseases such as cancer, rheumatoid arthritis, and haemophilia.

"Carboxamide" means the radical  $-C(O)NH_2$ .

"Carbamoyl" or "aminocarbonyl" means the radical  $-C(O)NRR'$  where R and R' are independently selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl provided one of R and R' is not hydrogen.

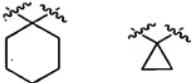
20 "Carboxy" means the radical  $-C(O)OH$ .

"Carboxyalkyl" means the radical  $-(alkylene)-C(O)OH$  e.g., carboxymethyl, carboxyethyl, and the like.

25 "Cycloalkyl" means a monovalent saturated or partially unsaturated, monocyclic, fused bicyclic ring assembly containing three to eight ring carbon atoms e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, and the like.

"Cycloalkylalkyl" means the radical  $-(alkylene)-R$  where R is cycloalkyl as defined above e.g., cyclopropylmethyl, cyclobutylethyl, cyclobutylmethyl, and the like

30 "Cycloalkylene" means a divalent saturated or partially unsaturated monocyclic ring or fused ring assembly containing three to eight ring carbon atoms. For example, the instance wherein "R<sup>5</sup> and R<sup>6</sup> together with the carbon atom to which both R<sup>5</sup> and R<sup>6</sup> are attached form cycloalkylene" includes, but is not limited to, the following:



, and the like.

"Disubstituted amino" means a radical  $-NRR'$  where R is alkyl, aryl, aralkyl, heteroaryl, heteraralkyl, or heterocycloalkyl, and R' is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, hydroxalkyl, alkoxyalkyl, or acyl. Representative examples include, but are not limited to, dimethylamino, methylphenylamino, benzylmethylamino, acetyl/methylamino, and the like.

"Derived" means a similar agent can be traced to.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Deleterious immune response" means an immune response that prevents effective treatment of a patient or causes disease in a patient. As an example, dosing a patient with murine antibody either as a therapy or a diagnostic agent causes the production of human antimouse antibodies that prevent or interfere with subsequent treatments. The incidence of antibody formation versus pure murine monoclonals can exceed 70%. (see Khazaeli, M. B. et al. "Human immune response to monoclonal antibodies", *J. Immunother.* 1994, 15, 42-52; Dillman R. O. et al. "Human anti-mouse antibody response in cancer patients following single low-dose injections of radiolabeled murine monoclonal antibodies". *Cancer Biother.* 1994, 9, 17-28; and Reinsberg, J. "Interference by human antibodies with tumor marker assays". *Hybridoma.* 1995, 14, 205-208). Additional examples of known agents that suffer from deleterious immune responses are blood-clotting factors such as factor VIII. When administered to hemophilia A patients, factor VIII restores the ability of the blood to clot. Although factor VIII is a human protein, it still elicits an immune response in hemophiliacs as endogenous factor VIII is not present in their blood and thus it appears as a foreign antigen to the immune system. Approximately 29-33% of new patients will produce antibodies that bind and neutralize the therapeutically administered factor VIII (see Lusher J. M. First and second generation recombinant factor VIII concentrates in previous untreated patients: recovery, safety efficacy, and inhibitor development. *Semin Thromb Hemost.* 2002, 28(3), 273-276). These neutralizing antibodies require the administration of larger amounts of factor VIII in order to maintain normal blood

clotting parameters; an expensive regimen of treatment in order to induce immune tolerance (see Briet E et al. The incidence of inhibitors in hemophilia A and the induction of immune tolerance. *Adv. Exp. Med. Bio.* 2001, 489, 89-97). Another immunogenic example is adenoviral vectors. Retroviral therapy remains experimental and is of limited utility. One reason is that the

5 application of a therapeutic virus generates an immune response capable of blocking any subsequent administration of the same or similar virus (see Yiping Yang et al. Cellular and Humoral Immune Responses to Viral Antigen Create Barrier to Lung-Directed Gene Therapy with Recombinant Adenoviruses. *J. of Virology.* 1995, 69, 2004-2015). This ensures that retroviral therapies must be based on the transient expression of a protein or the direct incorporation of viral

10 sequence into the host genome. Directed research has identified multiple viral neutralizing epitopes recognized by host antibodies (see Hanne, Gahery-Segard et al. Immune Response to Recombinant Capsid Proteins of Adenovirus in Humans: Antifiber and Anti-Penton Base Antibodies has a Synergistic Effect on Neutralizing Activity. *J. of Virology* 1998, 72, 2388-2397) suggesting that viral modifications will not be sufficient to overcome this obstacle. This invention

15 will enable a process whereby an adenoviral therapy will have utility for repeated application. Another example of an immunogenic agent that elicits neutralizing antibodies is the well-known cosmetic agent Botox. Botulin toxin protein, is purified from the fermentation of *Clostridium botulinum*. As a therapeutic agent, it is used for muscle disorders such as cervical dystonia in addition to cosmetic application. After repeated exposure patients generate neutralizing antibodies

20 to the toxin that results in reduced efficacy (see Birklein F. et al. Sudomotor testing predicts the presence of neutralizing botulinum A toxin antibodies. *Ann Neurol.* 2002, 52, 68-73 and Rollnik, J. D. et al. Neutralizing botulinum toxic type a antibodies: clinical observations in patient with cervical dystonia. *Neurol. Clin. Neurophysiol.* 2001, 2001(3), 2-4). A "deleterious immune response" also encompasses diseases caused by therapeutic agents. A specific example of this is

25 the immune response to therapy with recombinant human erythropoietin (EPO). Erythropoietin is used to stimulate the growth of red cells and restore red blood cell counts in patients who have undergone chemotherapy or dialysis. A small percentage of patients develop antibodies to EPO and subsequently are unresponsive to both therapeutically administered EPO and their own endogenous EPO (see Casadevall, N. et al., Pure red-cell aplasia and anti-erythropoietin antibodies

30 in patients treated with recombinant erythropoietin. *NEJM.* 2002, 346:469-475). They contract a disorder, pure red cell aplasia, in which red blood cell production is severely diminished (see Gershon S. K. et. al. Pure red-cell aplasia and recombinant erythropoietin. *NEJM.* 2002, 346:1584-

1586). This complication of EPO therapy is lethal if untreated. Another specific example is the murine antibody, OKT3 (a.k.a., Orthoclone) a monoclonal antibody directed towards CD-3 domain of activated T-cells. In clinical trials 20-40% of patients administered OKT3 produce antibodies versus the therapy. These antibodies besides neutralizing the therapy also stimulate a 5 strong host immune reaction. The immune reaction is severe enough that patients with high titers of human anti-mouse antibodies are specifically restricted from taking the drug (see Orthoclone package label). A final example is a human antibody therapeutic. Humira® is a monoclonal antibody directed against TNF and is used to treat rheumatoid arthritis patients. When taken alone ~12% of patients develop neutralizing antibodies. In addition, a small percentage of patients given 10 the drug also contract a systemic lupus erthematosus-like condition that is an IgG-mediated immune response induced by the therapeutic agent (see Humira package label).

Another example of "deleterious immune response" is a host reaction to small molecule drugs. It is known to the those skilled in the art that certain chemical structures will conjugate with host proteins to stimulate immune recognition (see Ju. C. et al. 2002. Current Drug 15 Metabolism 3, 367-377 and Kimber I. et al. 2002, Toxicologic Pathology 30, 54-58.) A substantial portion of this host reactions are IgG mediated. Specific "deleterious immune responses" that are IgG mediated and include: hemolytic anemia, Steven-Johnson syndrome and drug induced Lupus.

20 "Halo" means fluoro, chloro, bromo or iodo.  
"Haloalkyl" means alkyl substituted by one or more, preferably one to five, "halo" atoms, as such terms are defined in this Application. Haloalkyl includes monohaloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like e.g. chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

25 "Haloalkoxy" refers to a radical -OR where R is haloalkyl group as defined above e.g., trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, and the like.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring of 5 to 10 ring atoms in which one or more, preferably one, two, or three, of the ring atoms are selected from nitrogen, oxygen or sulfur, the remaining ring atoms being carbon. Representative heteroaryl rings include, 30 but are not limited to, pyrrolyl, furanyl, thieryl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, benzofuranyl,

benzothienyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxaliny, pyrazolyl, and the like.

"Heteroaralkyl" means a radical -(alkylene)-R where R is heteroaryl as defined above e.g., pyridinylmethyl, 1- or 2-furanylethyl, imidazolylmethyl, and the like.

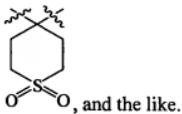
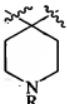
5 "Heteroaryloxyalkyl" means the radical -(alkylene)-OR where R is heteroaryl as defined above e.g., furanyloxyethyl, 2-, or 3-indolyloxyethyl, and the like.

"Heteroarylsulfonyl" refers to a radical  $-\text{SO}_2\text{R}$  where R is an heteroaryl group e.g., pyridinylsulfonyl, and the like.

10 "Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more, preferably one, two, or three of the ring carbon atoms indicated are replaced by a heteroatom selected from -N-, -O-, -S-, -SO-, or  $-\text{S}(\text{O})_2-$  and additionally one or two carbon atoms are optionally replaced by  $-\text{C}(\text{O})-$ . Representative examples include, but are not limited to, imidazolidinyl, morpholinyl, thiomorpholinyl, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyranyl, 1,1-dioxotetrahydropyranyl, indolinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like.

15 "Heterocycloalkylalkyl" means -(alkylene)-heterocycloalkyl as defined in this Application. Representative examples include, but are not limited to, imidazolidin-1-ylmethyl, morpholin-4-ylmethyl, thiomorpholin-4-ylmethyl, thiomorpholin-4-ylmethyl-1-oxide, indolinylethyl, piperazinylmethyl or ethyl, piperidylmethyl or ethyl, pyrrolidinylmethyl or ethyl, and the like.

20 "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more, preferably one or two, of the ring member carbon atoms is replaced by a heteroatom selected from -N-, -O-, -S-, or  $-\text{S}(\text{O})_2-$  and optionally one or two ring member carbon atoms are replaced with  $-\text{C}(\text{O})-$ . For example, the instance wherein  $\text{R}^5$  and  $\text{R}^6$  together with the carbon atom 25 to which both  $\text{R}^5$  and  $\text{R}^6$  are attached form heterocycloalkylene" includes, but is not limited to, the following:



in which R is a substituent defined in the Summary of the Invention

"Hydroxy" means the radical -OH.

"Hydroxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two

5 hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, 10 preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

"Isomers" mean compounds of the present invention having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and

15 stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has  $2^{n-1}$  enantiomeric pairs, where  $n$  is the number of chiral centers. Compounds with more than one chiral 20 center may exist as either an individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the R- and

25 S-sequencing rules of Cahn, Ingold and Prelog. For example, the stereochemistry at the carbon to which R<sup>1a</sup> are attached is (S) when the Prelog rule places the order of the substituent 1) N, 2) -COOH, 3) R<sup>1a</sup> and 4) H; and (R) when the Prelog rule places the order of the substituent 1) N, 2) R<sup>1a</sup>, 3) -COOH and 4) H.

Conventions for stereochemical nomenclature, methods for the determination of

30 stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is

understood that the names and illustration used in this Application to describe compounds of Formula () are meant to be encompassed all possible stereoisomers.

Additionally, compounds of Formula (I) may exist as tautomers. Such tautomeric forms (individual tautomers or mixtures thereof) are within the scope of this invention.

5 "Keto or oxo" means the radical (=O).

"Monosubstituted amino" means a radical  $-NHR$  where R is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, or acyl as defined herein. Representative examples include, but are not limited to, methylamino, phenylamino, benzylamino, cycloalkylmethylamino, acetylamino, trifluoroacetyl, and the like.

10 "Nitro" means the radical  $-NO_2$ .

"Optional" or "optionally" or "may be" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "wherein the aromatic ring  $R^8$  is optionally substituted with one or two substituents independently selected from alkyl" means that the aromatic ring may or may not be substituted with alkyl in order to fall within the scope of the invention. Additionally, the phrase "wherein  $R^{33}$  and  $R^{34}$  together with Si form a heterocycloalkylene ring containing a Si atom and 3 to 7 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with  $-NH-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-CO-$ ,  $-CONH-$ , or  $-SO_2NH-$  and wherein the heterocycloalkylene ring in  $R^{18}$  is optionally substituted on the ring with one, two, or three  $R^6$  independently selected from alkyl means the hydrogen on  $-NH-$  group may or may not be substituted with alkyl in order to fall within the scope of the invention.

20 The present invention also includes *N*-oxide derivatives of the compounds of this invention. *N*-oxide derivatives means derivatives of compounds of the present invention in which nitrogens are in an oxidized state (i.e.,  $N \rightarrow O$ ) e.g., pyridine *N*-oxide, and which possess the desired pharmacological activity.

25 "Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

30 "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired

pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, 5 malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methylsulfonic acid, ethanesulfonic acid, 1,2-ethanesulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 10 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable 15 inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

The present invention also includes prodrugs of a compound of the present invention. Prodrug means a compound that is convertible in vivo by metabolic means (e.g. by hydrolysis) to 20 a compound of the present invention. For example an ester of a compound of the present invention containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of the present invention containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of the present invention containing a hydroxy group, are for example acetates, 25 citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-*b*-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methylsulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinates. Suitable esters of compounds of the present invention containing a carboxy group, are for example those described by Leinweber, F.J. Drug Metab. Res., 30 1987, 18, pg. 379. An especially useful class of esters of compounds of the present invention containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 1989, 32, page 2503-2507, and include substituted

(aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and

5 (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of the present invention in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of the present invention are useful in the preparation of compounds of the present invention or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable 10 protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" means any administration of a compound of the present

15 invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the disease (i.e., arresting further development of the pathology and/or 20 symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the disease (i.e., reversing the pathology and/or symptomatology).

"Treatment" or "treating" with respect to combination therapy i.e., use with a biologic means any administration of a compound of the present invention and includes:

25 (1) preventing the immune response from occurring in an animal which may be predisposed to the immune response but does not yet experience or display the pathology or symptomatology of the immune response,

(2) inhibiting the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., arresting further development of the 30 pathology and/or symptomatology), or

(3) ameliorating the immune response in an animal that is experiencing or displaying the pathology or symptomatology of the immune response (i.e., reducing in degree or severity, or

extent or duration, the overt manifestations of the immune response or reversing the pathology and/or symptomatology e.g., reduced binding and presentation of antigenic peptides by MHC class II molecules, reduced activation of T-cells and B-cells, reduced humoral and cell-mediated responses and, as appropriate to the particular immune response, reduced inflammation, 5 congestion, pain, necrosis, reduced loss in the efficacy of a biologic agent, and the like).

#### Preferred Embodiments

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of this invention are preferred. For example:

10 A. One preferred group of compounds is that wherein E is  $-C(R^5)(R^6)X^1$  in which:  
 $R^5$  is hydrogen or alkyl; and  
 $R^6$  is hydrogen, alkyl, -(alkylene)-OR<sup>12</sup> (where R<sup>12</sup> is hydrogen, alkyl or haloalkyl), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl or heterocycloalkylalkyl is optionally substituted with one, two, or three R<sup>8</sup> independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, 15 monosubstituted amino, disubstituted amino, or acyl.

Preferably,  $R^5$  is hydrogen;  
 $R^6$  is alkyl, preferably ethyl or propyl, more preferably ethyl; and

20  $X^1$  is  $-CHO$ ,  $-C(O)R^{10}$ ,  $-C(O)CF_3$ ,  $-C(O)CF_2CF_2R^9$ ,  $-CH=CHS(O)_2R^{10}$ ,  $-C(O)CF_2C(O)NR^{10}R^{11}$ ,  $-C(O)C(O)NR^{10}R^{11}$ ,  $-C(O)CH_2OR^{10}$ ,  $-C(O)CH_2N(R^{11})SO_2R^{10}$ ,  $-C(O)C(O)N(R^{11})(CH_2)_2OR^{11}$ ,  $-C(O)C(O)N(R^{11})(CH_2)_2NHR^{11}$  or  $-C(O)C(O)R^{10}$  wherein R<sup>10</sup> is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl wherein the aromatic ring in R<sup>10</sup> is optionally substituted with R<sup>d</sup> selected from heteroaryl, aryl, alkyl, or 25 alkoxyalkyl R<sup>11</sup> is hydrogen or alkyl and R<sup>9</sup> is halo.

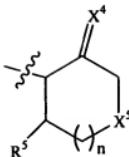
More preferably,

E is  $-CHR^6C(O)R^{10}$  where R<sup>6</sup> is alkyl, preferably ethyl, propyl, or butyl, more preferably ethyl, and R<sup>10</sup> is heteroaryl optionally substituted with one or two R<sup>d</sup> independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, 30 alkoxy carbonyl, aryl, heteroaryl, amino, monosubstituted amino, disubstituted amino, or acyl wherein the aromatic or alicyclic ring in R<sup>d</sup> is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy,

carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino. More preferably,  $R^{10}$  is benzoxazol-2-yl, 4-azabenzoxazol-2-yl, 2-pyridin-3-yl-[1,3,4]-oxadiazol-5-yl, 2-pyridin-4-yl-[1,3,4]-oxadiazol-5-yl, 2-ethyl-[1,3,4]-oxadiazol-5-yl, 2-isopropyl-[1,3,4]-oxadiazol-5-yl, 2-*tert*-butyl-[1,3,4]-oxadiazol-5-yl, 2-phenyl-[1,3,4]-oxadiazol-5-yl, 2-methoxymethyl-[1,3,4]-oxadiazol-5-yl, 2-furan-2-yl-[1,3,4]-oxadiazol-5-yl, 2-thien-2-yl-[1,3,4]-oxadiazol-5-yl, 2-(4-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(3-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(3-trifluoromethoxy-phenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-dimethylaminophenyl)-[1,3,4]-oxadiazol-5-yl, pyridazin-3-yl, pyrimidin-2-yl, 3-phenyl-[1,2,4]-oxadiazol-5-yl, 3-ethyl-[1,2,4]-oxadiazol-5-yl, 3-cyclopropyl-[1,2,4]-oxadiazol-5-yl, 3-thien-3-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-4-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-2-yl-[1,2,4]-oxadiazol-5-yl, 5-ethyl-[1,2,4]-oxadiazol-3-yl, 5-phenyl-[1,2,4]-oxadiazol-3-yl, 5-thien-3-yl-[1,2,4]-oxadiazol-3-yl, 5-trifluoromethyl-[1,2,4]-oxadiazol-3-yl, 5-pyridin-4-yl-[1,2,4]-oxadiazol-3-yl, or 5-phenyloxazol-2-yl. Even more preferably,  $R^{10}$  is benzoxazol-2-yl, oxazolo[4,5-b]pyridin-2-yl, 2-ethyl-[1,3,4]-oxadiazol-5-yl, 2-phenyl-[1,3,4]-oxadiazol-5-yl, 3-phenyl-[1,2,4]-oxadiazol-5-yl, 3-thien-3-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-3-yl-[1,2,4]-oxadiazol-5-yl, 3-ethyl-[1,2,4]-oxadiazol-5-yl, 5-ethyl-[1,2,4]-oxadiazol-3-yl, or 2-methoxymethyl-[1,3,4]-oxadiazol-5-yl. Most preferably  $R^{10}$  is benzoxazol-2-yl.

20 B. Another preferred group of compounds is that wherein E is  $-C(R^5)(R^6)X^1$  in which  $R^5$  and  $R^6$  taken together with the carbon atom to which both  $R^5$  and  $R^6$  are attached form cycloalkylene or heterocycloalkylene, preferably cyclopropylene, cyclopentylene, cyclohexylene, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-4-yl-1-oxide, tetrahydrothiopyran-4-yl-1,1-dioxide, or piperidin-4-yl wherein the nitrogen atom is optionally substituted with alkyl, alkoxy, or hydroxy, preferably tetrahydrothiopyran-4-yl-1,1-dioxide, and  $X^1$  is  $-CHO$ ,  $-C(O)R^{10}$ ,  $-C(O)CF_3$ ,  $-C(O)CF_2CF_2R^9$ ,  $-CH=CHS(O)_2R^{10}$ ,  $-C(O)CF_2C(O)NR^{10}R^{11}$ ,  $-C(O)C(O)NR^{10}R^{11}$ ,  $-C(O)CH_2OR^{10}$ ,  $-C(O)CH_2N(R^{11})SO_2R^{10}$ ,  $-C(O)C(O)N(R^{11})(CH_2)_2OR^{11}$ ,  $-C(O)C(O)N(R^{11})(CH_2)_2NR^1$  or  $-C(O)C(O)R^{10}$ . More preferably,  $X^1$  is  $-C(O)C(O)NR^{10}R^{11}$  where  $R^{11}$  is hydrogen and  $R^{10}$  is benzyl.

25 C. Yet another preferred group of compounds is that wherein E is a group of formula (a):



in which:

n is 0, 1, or 2, X<sup>4</sup> is -NR<sup>22</sup>-, -O- or -S- where R<sup>22</sup> is hydrogen, alkyl, or alkoxy; X<sup>5</sup> is -O-, -S(O)<sub>2</sub>-, -S- or -NR<sup>23</sup>- where R<sup>23</sup> is selected from hydrogen, alkyl, -S(O)<sub>2</sub>R<sup>24</sup>, -C(O)OR<sup>26</sup>, or acyl,

5 - where R<sup>24</sup> is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl and R<sup>26</sup> is hydrogen or alkyl.  
 Preferably, X<sup>4</sup> is -O-, n is 0 or 1, and X<sup>5</sup> is -O-.

D. Yet another preferred group of compounds is that wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> are hydrogen.

E. Yet another preferred group of compounds is that wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cycloalkylene optionally substituted with one or two R<sup>b</sup> independently selected from alkyl, halo, dialkylamino, aryl, aralkyl, 15 cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxycarbonyl.

Preferably, R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene optionally substituted with groups described immediately above. More preferably, R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene,

20 cycloheptylene, 2-methylcyclopropylene, 3-benzylcyclopentylene, 3-cyclohexylmethylcyclopentylene, 3-cyclopentylmethylcyclopentylene, 3-phenylcyclopentylene, 3-cyclohexylcyclopentylene, 3-cyclopentylcyclopentylene, 3-pyridin-2-ylmethylcyclopentylene, 3-pyridin-3-ylmethylcyclopentylene, 3-pyridin-4-ylmethylcyclopentylene, 2-methylcyclopropylene, 2,3-dimethylcyclopropylene, 3-benzylcyclobutylene, 3-methylcyclopentylene, 3,4-

25 dimethylcyclopentylene, 3-ethylcyclopentylene, 3-(1,1-dimethylpropyl)-cyclopentylene, 3-n-butylcyclopentylene, 3-ethoxycarbonylcyclopentylene, 3,4-diethoxycarbonyl-cyclopentylene, or 3-benzyl-4-dimethylaminocyclopentylene. Most preferably, R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cyclopropylene.

F. Yet another preferred group of compounds is that wherein E is  $-\text{CR}^{5a}\text{R}^{6a}\text{CN}$  wherein  $\text{R}^{5a}$  and  $\text{R}^{6a}$  together with the carbon atom to which they are attached form heterocycloalkylene optionally substituted with one to four alkyl or one or two  $\text{R}^c$  which are independently selected

5 from alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl,  $-\text{S}(\text{O})_{n2}\text{R}^{14}$ ,  $-\text{alkylene-S(O)}_{n2}\text{R}^{15}$ ,  $-\text{COOR}^{16}$ ,  $-\text{alkylene-COOR}^{17}$ ,  $-\text{CONR}^{18}\text{R}^{19}$ , or  $-\text{alkylene-CONR}^{20}\text{R}^{21}$  (where  $n2$  is 0-2 and  $\text{R}^{14}\text{-R}^{17}$ ,  $\text{R}^{18}$  and  $\text{R}^{20}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,

10  $\text{R}^{19}$  and  $\text{R}^{21}$  are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, or acyl. Preferably,  $\text{R}^{5a}$  and  $15 \text{R}^{6a}$  together with the carbon atom to which they are attached form pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiopyran-4-yl-1-oxide, tetrahydrothiopyran-4-yl-1,1-dioxide, hexahydropyridimidinyl, or hexahydropyridazinyl optionally substituted as described above. More preferably,  $\text{R}^{5a}$  and  $\text{R}^{6a}$  together with the carbon atom to which they are attached form piperidin-4-yl substituted with one to three alkyl and one  $\text{R}^c$  selected

20 from haloalkyl, aminoalkyl, alkoxy carbonyl, alkoxyalkyl, alkoxyalkyloxyalkyl, heterocycloalkyl, heterocycloalkylalkyl,  $-\text{alkylene-CONR}^{20}\text{R}^{21}$ , or cycloalkyl wherein the alicyclic ring is optionally substituted with substituents listed above. Most preferably,  $\text{R}^{5a}$  and  $\text{R}^{6a}$  together with the carbon atom to which they are attached form piperidin-4-yl optionally substituted at the 1-position with methyl, ethyl, propyl, *n*-butyl, *n*-pentyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 3-

25 morpholin-4-ylpropyl, 3-piperidin-1-yl-propyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(1-methylpiperidin-4-yl)propyl, 4-morpholin-4-ylbutyl, 2-(2-methoxyethoxy)ethyl, 4-methoxybutyl, 4-aminocarbonylbutyl, 3-aminocarbonylpropyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 1-ethoxycarbonylpiperidin-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, hydroxy, 2,2,2-trifluoroethyl, or *tert*-butyl, 1,2-dimethylpiperidin-4-yl, 1,2,6-trimethylpiperidin-4-yl, 1,2,2-trimethylpiperidin-4-yl, 1-methyl-2-oxopiperidin-4-yl, 1-methylpiperidin-3-yl, 1-*tert*-butoxycarbonylpiperidin-4-yl, 1-cyclohexylpiperidin-4-yl, 1-cyclopropylmethylpyrrolidin-3-yl, 1-benzylpyrrolidin-3-yl, 1-benzylloxycarbonylpiperidin-3-yl, pyrrolidin-3-yl, 1-hydroxypyrrrolidin-

30

3-yl, 1-methylpyrrolidin-3-yl, 1-ethypyrrrolidin-3-yl, 1-*n*-propyl or *n*-butylpyrrolidin-3-yl, 1-cyclohexylpyrrolidin-3-yl, 1-ethyl-2,2-dimethylpyrrolidin-4-yl, 1-propyl-2-methoxycarbonylpiperidin-4-yl, 2-oxypyrrrolidin-3-yl, 1-ethyl-2-oxopyrrrolidin-3-yl, morpholin-4-yl, 1-(1-methylpiperidin-4-ylcarbonyl)piperidin-4-yl, 1-ethoxycarbonylpiperidin-4-yl, 1-5 benzylazetidin-3-yl, tetrahydrothiopyran-4-yl-1-oxide, or tetrahydrothiopyran-4-yl-1,1-dioxide. Particularl preferably, R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form piperidin-4-yl substituted at the 1-position with ethyl, *n*- or 2-propyl, tetrahydrothiopyran-4-yl tetrahydrothiopyran-4-yl-1,1-oxide, or tetrahydrothiopyran-4-yl-1,1-dioxide. Even more particularly preferably, R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form 10 piperidin-4-yl substituted at the 1-position with ethyl, *n*- or 2-propyl or tetrahydrothiopyran-4-yl-1,1-dioxide.

(a) Within the above preferred and more preferred groups (A-F), an even more preferred group of compounds is that wherein R<sup>1</sup> and R<sup>2</sup> are hydrogen.

15 (i) Within these preferred, more preferred, and even more preferred groups, a more preferred group of compounds is that wherein Q is -CO-.

(ii). Within these preferred, more preferred, and even more preferred groups, another more preferred group of compounds is that wherein Q is -OCO-.

(iii). Within these preferred, more preferred, and even more preferred groups, yet another more preferred group of compounds is that wherein Q is -NHCO-.

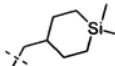
20 (iv). Within these preferred, more preferred, and even more preferred groups, yet another more preferred group of compounds is that wherein Q is -CH(CF<sub>3</sub>)-.

Within the above preferred, more preferred, and even more preferred groups above, a particularly preferred group of compounds is that wherein:

25 R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl, R<sup>33</sup> is alkyl, and R<sup>34</sup> is alkyl. Preferably, R<sup>32</sup>, R<sup>33</sup>, and R<sup>34</sup> are independently methyl, ethyl, *n*-propyl, isopropyl, butyl, *sec*-butyl, or *tert*-butyl. More preferably, R<sup>1a</sup> is -CH<sub>2</sub>-Si(CH<sub>3</sub>)<sub>3</sub> or -CH<sub>2</sub>-Si(2-methylpropyl)(CH<sub>3</sub>)<sub>2</sub>. Even more preferably, R<sup>1a</sup> is -CH<sub>2</sub>-Si(CH<sub>3</sub>)<sub>3</sub>.

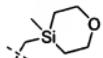
Within the above preferred, more preferred, and even more preferred groups above, 30 another particularly preferred group of compounds is that wherein:

R<sup>1a</sup> is a group having the structure:

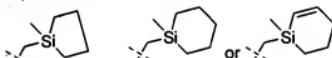


Within the above preferred, more preferred, and even more preferred groups above, another particularly preferred group of compounds is that wherein:

5 R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl and R<sup>33</sup> and R<sup>34</sup> together with Si form a heterocycloalkylene ring containing a Si atom and 4 or 5 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with -NH-, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CONH-, or -SO<sub>2</sub>NH-. Preferably, R<sup>1a</sup> is a group having the structure:

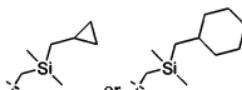


Preferably, R<sup>1a</sup> is a group having the structure:



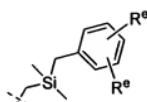
10 Within the above preferred, more preferred, and even more preferred groups above, another particularly preferred group of compounds is that wherein:

R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> and R<sup>33</sup> are alkyl and R<sup>34</sup> is cycloalkylalkyl. Preferably, R<sup>1a</sup> is a group having the structure:



15 Within the above preferred, more preferred, and even more preferred groups above, another particularly preferred group of compounds is that wherein:

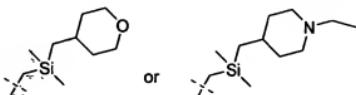
R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> and R<sup>33</sup> are alkyl and R<sup>34</sup> is aralkyl. Preferably, R<sup>1a</sup> is a group having the structure:



20 where each R<sup>e</sup> is independently selected from hydrogen, alkyl, haloalkyl, haloalkoxy, or alkoxy.

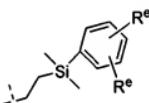
Within the above preferred, more preferred, and even more preferred groups above, yet another particularly preferred group of compounds is that wherein:

$R^{1a}$  is  $-(\text{alkylene})-\text{Si}R^{32}R^{33}R^{34}$  where  $R^{32}$  and  $R^{33}$  are alkyl and  $R^{34}$  is heteroaralkyl optionally substituted with  $R^e$ . Preferably,  $R^{1a}$  is a group having the structure:



Within the above preferred, more preferred, and even more preferred groups above, yet 5 another particularly preferred group of compounds is that wherein:

$R^{1a}$  is  $-(\text{alkylene})-\text{Si}R^{32}R^{33}R^{34}$  where  $R^{32}$  and  $R^{33}$  are alkyl and  $R^{34}$  is aryl. Preferably,  $R^{1a}$  is a group having the structure:



where each  $R^e$  is independently selected from hydrogen, alkyl, haloalkyl, haloalkoxy, or alkoxy.

10 Within the above preferred, more preferred, even more preferred, and particularly preferred group of compounds, a more particularly preferred group is that wherein  $R^3$  is alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl, preferably, aryl, heteroaryl, or heterocycloalkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or 15 heteroaryl ring is optionally substituted with one or two  $R^f$ .

Within the above preferred, more preferred, even more preferred, and particularly preferred group of compounds, a more particularly preferred group is that wherein  $R^3$  is a group selected from methyl, cyclohexylmethyl, 3-cyclohexylpropyl, 2-cyclohexylethyl, 2-cyclopentylethyl, 6-hydroxypyrid-3-yl, 1*H*-imidazol-4-yl, morpholin-4-yl, naphth-1-ylmethyl, 2-phenylethyl, 20 piperazin-1-yl, piperidin-4-yl, pyrazin-2-yl, pyridin-3-yl, pyridin-4-yl, and tetrahydropyran-4-yl.

Within the above preferred, more preferred, even more preferred, and particularly preferred group of compounds, a more particularly preferred group is that wherein Q is  $-\text{CO-}$  and  $R^3$  is morpholin-4-yl, piperidin-4-yl, pyrazin-2-yl, pyridin-3-yl, pyridin-4-yl, or tetrahydropyran-4-yl.

25 G. Another preferred group of compounds of Formula (I) is that wherein:

$R^{1a}$  is  $-(\text{alkylene})-\text{Si}R^{32}R^{33}R^{34}$  where  $R^{32}$  is alkyl,  $R^{33}$  is alkyl, and  $R^{34}$  is alkyl. Preferably,

R<sup>32</sup>, R<sup>33</sup>, and R<sup>34</sup> are independently methyl, ethyl, *n*-propyl, isopropyl, butyl, *sec*-butyl, or *tert*-butyl. More preferably, R<sup>1a</sup> is -CH<sub>2</sub>-Si(CH<sub>3</sub>)<sub>3</sub> or -CH<sub>2</sub>-Si(2-methylpropyl)(CH<sub>3</sub>)<sub>2</sub>. Even more preferably, R<sup>1a</sup> is -CH<sub>2</sub>-Si(CH<sub>3</sub>)<sub>3</sub>.

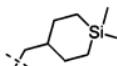
Within this group, a more preferred group of compounds is that wherein:

5 Q is -CO-; and

R<sup>1</sup> and R<sup>2</sup> are hydrogen.

H. Another preferred group of compounds of Formula (I) is that wherein:

R<sup>1a</sup> is a group having the structure:



10

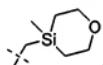
Within this group, a more preferred group of compounds is that wherein:

Q is -CO-; and

R<sup>1</sup> and R<sup>2</sup> are hydrogen.

15 I. Another preferred group of compounds of Formula (I) is that wherein:

R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl and R<sup>33</sup> and R<sup>34</sup> together with Si form a heterocycloalkylene ring containing a Si atom and 4 or 5 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with -NH-, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CONH-, or -SO<sub>2</sub>NH-. Preferably, R<sup>1a</sup> is a group having the structure:



20

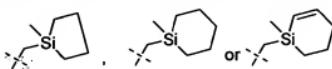
Within this group, a more preferred group of compounds is that wherein:

Q is -CO-; and

R<sup>1</sup> and R<sup>2</sup> are hydrogen.

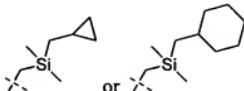
25 J. Another preferred group of compounds of Formula (I) is that wherein:

R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl and R<sup>33</sup> and R<sup>34</sup> together with Si form a heterocycloalkylene ring. Preferably, R<sup>1a</sup> is a group having the structure:



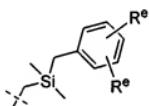
Within this group, a more preferred group of compounds is that wherein:  
Q is  $-\text{CO}-$ ; and  
 $\text{R}^1$  and  $\text{R}^2$  are hydrogen.

5 K. Another preferred group of compounds of Formula (I) is that wherein:  
 $\text{R}^{1a}$  is  $-(\text{alkylene})-\text{SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  and  $\text{R}^{33}$  are alkyl and  $\text{R}^{34}$  is cycloalkylalkyl.  
Preferably,  $\text{R}^{1a}$  is a group having the structure:



10 Within this group, a more preferred group of compounds is that wherein:  
Q is  $-\text{CO}-$ ; and  
 $\text{R}^1$  and  $\text{R}^2$  are hydrogen.

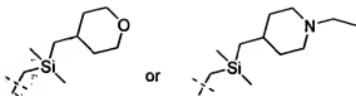
15 L. Another preferred group of compounds of Formula (I) is that wherein:  
 $\text{R}^{1a}$  is  $-(\text{alkylene})-\text{SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  and  $\text{R}^{33}$  are alkyl and  $\text{R}^{34}$  is aralkyl. Preferably,  
 $\text{R}^{1a}$  is a group having the structure:



where each  $\text{R}^6$  is independently selected from hydrogen, alkyl, haloalkyl, haloalkoxy, or alkoxy.

20 Within this group, a more preferred group of compounds is that wherein:  
Q is  $-\text{CO}-$ ; and  
 $\text{R}^1$  and  $\text{R}^2$  are hydrogen.

M. Another preferred group of compounds of Formula (I) is that wherein:  
 $\text{R}^{1a}$  is  $-(\text{alkylene})-\text{SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  and  $\text{R}^{33}$  are alkyl and  $\text{R}^{34}$  is heteroaralkyl  
25 optionally substituted with  $\text{R}^6$ . Preferably,  $\text{R}^{1a}$  is a group having the structure:



Within this group, a more preferred group of compounds is that wherein:

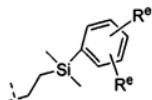
Q is  $-\text{CO}-$ ; and

$\text{R}^1$  and  $\text{R}^2$  are hydrogen.

5

N. Another preferred group of compounds of Formula (I) is that wherein:

$\text{R}^{1a}$  is  $-(\text{alkylene})-\text{SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  and  $\text{R}^{33}$  are alkyl and  $\text{R}^{34}$  is aryl. Preferably,  $\text{R}^{1a}$  is a group having the structure:



10 where each  $\text{R}^6$  is independently selected from hydrogen, alkyl, haloalkyl, haloalkoxy, or alkoxy.

Within this group, a more preferred group of compounds is that wherein:

Q is  $-\text{CO}-$ ; and

$\text{R}^1$  and  $\text{R}^2$  are hydrogen.

15 Within the above preferred and more preferred groups in (G-N), an even more preferred group of compounds is that wherein E is  $-\text{CHR}^6\text{C}(\text{O})\text{R}^{10}$  where  $\text{R}^6$  is alkyl, preferably ethyl, propyl, or butyl, more preferably ethyl, and  $\text{R}^{10}$  is heteroaryl optionally substituted with one or two  $\text{R}^d$  independently selected from alkyl, haloalkyl, alkoxy, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, aryl, heteroaryl, amino, monosubstituted amino, disubstituted 20 amino, or acyl wherein the aromatic or alicyclic ring in  $\text{R}^d$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino, more preferably  $\text{R}^{10}$  is benzoxazol-2-yl, 4-azabenzoxazol-2-yl, 2-pyridin-3-yl-[1,3,4]-oxadiazol-5-yl, 2-pyridin-4-yl-[1,3,4]-oxadiazol-5-yl, 2-ethyl-[1,3,4]-oxadiazol-5-yl, 2-isopropyl-[1,3,4]-oxadiazol-5-yl, 2-*tert*-25 butyl-[1,3,4]-oxadiazol-5-yl, 2-phenyl-[1,3,4]-oxadiazol-5-yl, 2-methoxymethyl-[1,3,4]-oxadiazol-5-yl, 2-furan-2-yl-[1,3,4]-oxadiazol-5-yl, 2-thien-2-yl-[1,3,4]-oxadiazol-5-yl, 2-(4-methoxy-phenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(3-methoxy-

phenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(3-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-dimethylaminophenyl)-[1,3,4]-oxadiazol-5-yl, pyradizin-3-yl, pyrimidin-2-yl, 3-phenyl-[1,2,4]-oxadiazol-5-yl, 3-ethyl-[1,2,4]-oxadiazol-5-yl, 3-cyclopropyl-[1,2,4]-oxadiazol-5-yl, 3-5  
thien-3-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-4-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-2-yl-[1,2,4]-oxadiazol-5-yl, 5-ethyl-[1,2,4]-oxadiazol-3-yl, 5-phenyl-[1,2,4]-oxadiazol-3-yl, 5-thien-3-yl-[1,2,4]-oxadiazol-3-yl, 5-trifluoromethyl-[1,2,4]-oxadiazol-3-yl, 5-pyridin-4-yl-[1,2,4]-oxadiazol-3-yl, or 5-phenyloxazol-2-yl. Even more preferably, R<sup>10</sup> is benzoazol-2-yl, oxazolo[4,5-b]pyridin-2-yl, 2-ethyl-[1,3,4]-oxadiazol-5-yl, 2-phenyl-[1,3,4]-oxadiazol-5-yl, 3-phenyl-[1,2,4]-oxadiazol-5-yl, 3-thien-3-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-3-yl-[1,2,4]-oxadiazol-5-yl, 3-ethyl-[1,2,4]-oxadiazol-5-yl, 5-ethyl-[1,2,4]-oxadiazol-3-yl, or 2-methoxymethyl-[1,3,4]-oxadiazol-5-yl.  
10

Within the above preferred and more preferred groups in (G-N), another even more preferred group of compounds is that wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cycloalkylene, preferably cyclopropylene.

15 Within the above preferred and more preferred groups in (G-N), another even more preferred group of compounds is that wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form heterocycloalkylene, preferably R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form piperidin-4-yl substituted at the 1-position with ethyl, *n*- or 2-propyl, tetrahydrothiopyran-4-yl tetrahydrothiopyran-4-yl-1-oxide, or  
20 tetrahydrothiopyran-4-yl-1,1-dioxide.

Within the above preferred, more preferred group, and even more preferred groups, a particularly preferred group of compounds is that wherein R<sup>3</sup> is aryl, heteroaryl, or heterocycloalkyl.

25 Additionally, in the preferred embodiments above, a number of different preferences have been given above, and following any one of these preferences results in a compound of this invention that is more presently preferred than a compound in which that particular preference is not followed. However, these preferences are generally independent; and following more than one of these preferences may result in a more presently preferred compound than one in which fewer of the preferences are followed.

30

## GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes

shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art

5 following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplements (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

10 These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation,

15 crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20

20 °C.

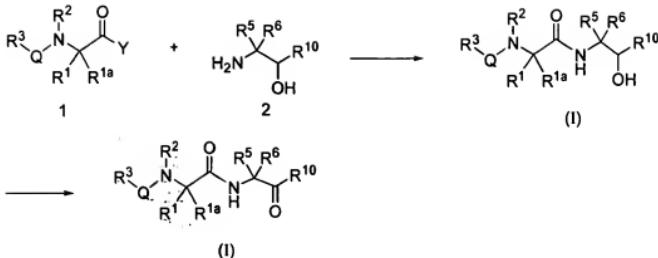
In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G.

25 M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Compound of Formula (I) can be prepared by the procedures described in Schemes 1-4 below.

Compounds of Formula (I) where E is  $-C(R^5)(R^6)C(R^7)(R^8)R^{10}$  and other groups are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 1 below:

30

Scheme 1



Reaction of a compound of formula 1 [where Y is hydroxy or an activating group (e.g.

2,5-dioxopyrrolidin-1-yl, succinimide, or the like), preferably hydroxy] with an aminoalcohol compound of formula 2 provides a compound of Formula (I) where R<sup>7</sup> is hydrogen and R<sup>8</sup> is hydroxy. The reaction conditions vary based on the nature of the Y group. When Y is an activating group, the reaction is carried out in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, or the like) and in a suitable solvent (e.g. acetonitrile, N,N-dimethylformamide (DMF), dichloromethane, or any suitable combination thereof, or the like) at 10 to 30°C, preferably at about 25°C, and requires 24 to 30 hours to complete. When Y is hydrogen a suitable coupling agent (e.g. benzotriazole-1- yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and a base (e.g. N,N-diisopropylethylamine, triethylamine, or the like) is required and the reaction takes about 2 to 3 hours to complete.

Compounds of formula 1 and 2 are either commercially available or they can be prepared by methods well known in the art. For example, compound 1 where Q is -CO- and Y is hydroxy can be readily prepared by reacting an amino acid of formula CR<sup>1</sup>R<sup>10</sup>(COOH)NHR<sup>2</sup> with an acylating agent of formula R<sup>3</sup>COL where L is a leaving group under acylating conditions such as a halo (particularly Cl or Br) or imidazolide. Suitable solvents for the reaction include aprotic polar solvents (e.g., dichloromethane, THF, dioxane and the like.). When an acyl halide is used as the acylating agent the reaction is carried out in the presence of a non-nucleophilic organic base e.g., triethylamine, pyridine, and the like. Acylating agents are either commercially available

or can be prepared by treating the corresponding acid with a chlorinating agent such as oxalyl chloride, sulfonyl chloride, and the like.

Compound 1 where Q is  $-\text{SO}_2-$  and Y is hydroxy can be readily prepared by reacting an amino acid of formula  $\text{CR}^1\text{R}^{1a}(\text{COOH})\text{NHR}^2$  with an with a sulfonyl halide, utilizing the reaction conditions described in method above. Sulfonyl halides are commercially available or may be prepared by methods such as those described in (1) Langer, R. F.; Can. J. Chem.; 61, 1583-1592, (1983); (2) Aveta, R.; et. al.; *Gazetta Chimica Italiana*, 116, 649-652, (1986); (3) King, J. F. and Hillhouse, J. H.; Can. J. Chem.; 54, 498, (1976); and (4) Szymonifka, M. J. and Heck, J. V.; *Tet. Lett.*; 30, 2869-2872, (1989).

Compound 1 where Q is  $-\text{NHCO}-$  and Y is hydroxy can be readily prepared by reacting an amino acid of formula  $\text{CR}^1\text{R}^{1a}(\text{COOH})\text{NHR}^2$  with an activating agent such as carbonyl diimidazole/thiocarbonyl diimidazole, followed by nucleophilic displacement of the imidazole group with a primary or secondary amine. The reaction occurs at ambient temperature. Suitable solvents include polar organic solvents (e.g., THF, dioxane and the like). Alternatively, these compounds can be prepared by reacting  $\text{CR}^1\text{R}^{1a}(\text{COOH})\text{NHR}^2$  with a carbamoyl halide. The reaction is carried out in the presence of a non-nucleophilic organic base. Suitable solvents for the reaction are dichloromethane, 1,2-dichloroethane, THF, or pyridine. These compounds can also be prepared by reacting  $\text{CR}^1\text{R}^{1a}(\text{COOH})\text{NHR}^2$  with an isocyanate in an aprotic organic solvent (e.g., benzene, THF, DMF and the like).

Compound 1 where Q is  $-\text{NHSO}_2-$  and Y is hydroxy can be readily prepared by reacting an amino acid of formula  $\text{CR}^1\text{R}^{1a}(\text{COOH})\text{NHR}^2$  with a sulfamoyl halide, utilizing the reaction conditions described in paragraph immediately above. Sulfamoyl halides are commercially available or may be prepared by methods such as those described in Graf, R; German Patent, 931225 (1952) and Catt, J. D. and Matler, W. L; *J. Org. Chem.*, 39, 566-568, (1974).

Compound 1 where Q is  $-\text{CHR}-$  where R is haloalkyl and Y is hydroxy can be readily prepared by reacting an amino acid of formula  $\text{CR}^1\text{R}^{1a}(\text{COOR}')\text{NHR}^2$  where R' is alkyl can be prepared by the methods disclosed in PCT application Publication No. WO 03/075836 the disclosure of which is incorporated herein by reference in its entirety.

Amino acids of formula  $\text{CR}^1\text{R}^{1a}(\text{COOH})\text{NHR}^2$  where  $\text{R}^1$ ,  $\text{R}^{1a}$  and  $\text{R}^2$  are defined in the

Summary of the Invention can be prepared by methods well known in the art. Detailed syntheses of an amino acid where  $\text{R}^1$  and  $\text{R}^2$  are hydrogen and  $\text{R}^{1a}$  is 2-trimethylsilylmethyl are provided in working examples below.

Compounds of formula 2 where  $R^{10}$  is benzoxazol-2-yl, oxazolo[4,5-b]pyridin-2-yl, and the like, can be prepared under deprotonation reaction conditions by treating benzoxazole, oxazolo[4,5-b]pyridine, 2-pyridin-3-yloxadiazole, 2-pyridin-4-yl-oxadiazole, 2-phenyloxadiazole, and the like, with a Grignard reagent such as isopropylmagnesium chloride and then reacting the resulting organomagnesium reagent with an alpha-(*N*-protected amino)aldehyde of formula  $CR^5R^6(NHPG)CHO$ , where PG is a suitable amino protecting group (such as *tert*-butoxycarbonyl, benzyloxycarbonyl, or benzyl) to provide a compound of formula  $CR^5R^6(NHPG)CH(R^{10})OH$  where  $R^{10}$  is benzoxazol-2-yl, oxazolo[4,5-b]pyridin-2-yl, 2-pyridin-3-yloxadiazolyl, 2-pyridin-4-yl-oxadiazolyl, 2-phenyloxadiazolyl, and the like, after treatment with an aqueous acid or buffer. Removal of the amino protecting group then provides a compound of formula 2 where  $R^{10}$  is benzoxazol-2-yl, oxazolo[4,5-b]pyridin-2-yl, 2-pyridin-3-yloxadiazolyl, 2-pyridin-4-yl-oxadiazolyl, 2-phenyloxadiazolyl, and the like.

The addition reaction is typically carried out in an ethereal organic solvent such as tetrahydrofuran, diethyl ether, dioxane, and the like, preferably tetrahydrofuran, at a temperature from about -78 °C to about 40 °C. Preferably, the reaction is carried out from about -10 °C to about 40 °C, more preferably from about -10 °C to about 10 °C. The reaction typically requires an hour to complete. The nucleophilic addition reaction is typically carried out from about -10 °C to about room temperature. Compounds of formula  $CR^5R^6(NHPG)CHO$  are prepared from commercially available starting materials by methods well known in the art.

Compounds of formula 2 can also be prepared by other methods known in the art. Some such methods are disclosed in working examples below.

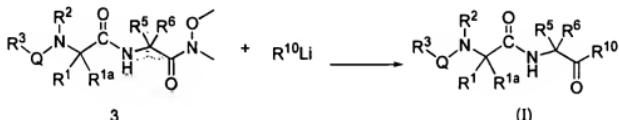
The reaction conditions employed for removal of the amino protecting group depends on the nature of the protecting group. For example, if the protecting group is *tert*-butoxycarbonyl, it is removed under acid reaction conditions. Suitable acids are trifluoroacetic acid (TFA), hydrochloric acid, and the like. If the protecting group is benzyl or benzyloxycarbonyl, it is removed under catalytic hydrogenation reaction conditions. Suitable catalyst are palladium, platinum, rhodium based catalysts and others known in the art. Other suitable reaction conditions for their removal can be found in Greene, T.W.; and Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*; John Wiley & Sons, Inc. 1999. The reaction is carried out in an inert organic solvent methylene chloride, tetrahydrofuran, dioxane, dimethylformamide, and the like.

Oxidation of hydroxy group in (I) where  $R^7$  is hydroxy and  $R^8$  is hydrogen with a suitable oxidizing agent such as Dess-Martin Periodinane in a halogenated organic solvent such as

methylene chloride, chloroform, carbon tetrachloride, and the like, or a mixture of TEMPO/bleach then provides a corresponding compound of Formula (I) where  $R^7$  and  $R^8$  together form oxo.

Alternatively, compounds of Formula (I) where E is  $-C(R^5)(R^6)C(R^7)(R^8)R^{10}$  where  $R^7$  and  $R^8$  together form oxo and other groups are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 2 below:

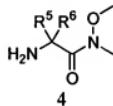
Scheme 2



10

Compounds of Formula (I) where  $R^7$  and  $R^8$  together form oxo can be prepared by reacting a compound of formula 3 with an organometallic compound of formula  $\text{R}^{10}\text{Li}$ . The reaction is carried out in a suitable solvent (e.g. tetrahydrofuran (THF), ether, or the like) at  $-80$  to  $-70^\circ\text{C}$ , preferably at about  $-78^\circ\text{C}$ , and requires 30 minutes to an hour to complete. The organometallic compound of formula  $\text{R}^{10}\text{Li}$  is generated by treating a corresponding organo compound or a brominated derivative thereof, with *n*-butyllithium or *tert*-butyllithium in a suitable solvent (e.g. THF, ether, or the like) at  $-80$  to  $-70^\circ\text{C}$ , preferably at about  $-78^\circ\text{C}$ , for approximately 30 minutes to an hour.

20 Compounds of formula 3 can be prepared by reacting an amino acid of formula 4



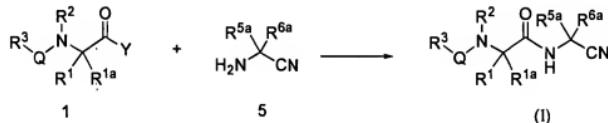
25 with a compound of the formula  $\text{R}^3\text{Q}(\text{R}^2)\text{C}(\text{R}^1)(\text{R}^{1a})\text{C}(\text{O})\text{Y}$  where Q and  $\text{R}^3$  are as defined in the Summary of the invention and Y is hydroxy or an activating group (succinimide, or the like) under conditions described in Scheme 1 above.

Compounds formula 4 can be prepared by reacting a corresponding *N*-protected alpha amino acid with *N,O*-dimethylhydroxylamine hydrochloride followed by deprotection of the amino group. The reaction with the *N,O*-dimethylhydroxylamine is carried out in the presence of

a suitable coupling agent (PyBOP®, EDC, HBTU, DCC, and the like) and a base (e.g. *N,N*-diisopropylethylamine, triethylamine, or the like) in a suitable solvent (e.g. dichloromethane, DMF, and the like) at 20 to 30° C, preferably at about 25° C, and takes about 2 to 4 hours to complete. Deprotection of the amino group provides the desired compound 4.

5 Compounds of Formula (I) where E is  $-\text{C}(\text{R}^{5a})(\text{R}^{6a})\text{CN}$  and other groups are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 3 below:

Scheme 3

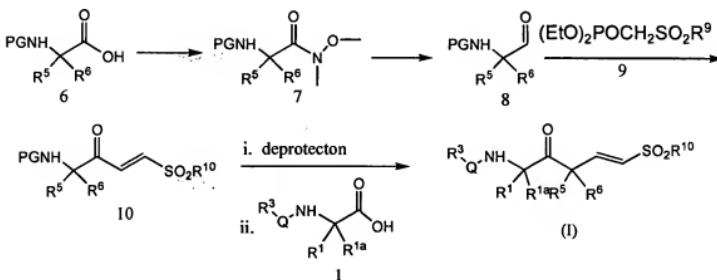


Reaction of a compound of formula 1 where Y is hydroxy or succinimide ester with an aminonitrile compound of formula 5 under the reaction conditions described in Scheme 1 above 15 provides a compound of Formula (I).

Compounds of Formula (I) where E is  $-\text{C}(\text{R}^5)(\text{R}^6)\text{CH}=\text{CHS}(\text{O})_2\text{R}^{10}$  and other groups are as defined in the Summary of the Invention can be prepared by proceeding as illustrated and described in Scheme 4 below:

20

Scheme 4



Reaction of an *N*-protected amino acid of formula 6 with *N,O*-dimethylhydroxylamine hydrochloride in the presence of 1 equivalent of triethylamine and *N,N*-dicyclohexylcarbodiimide forms the *N,O*-dimethylhydroxamate (Weinreb amide) 7, which is then reduced to the corresponding aldehyde 8 with a suitable reducing agent such as 0.5 equivalents of lithium

5 aluminum hydride.

Condensation of 8 with a Wadsworth-Emmons reagent  $(EtO)_2POCH_2SO_2R^1$  9 wherein  $R^{10}$  is as defined in the Summary of the Invention, affords the vinyl sulfone 10. Removal of the *N*-protecting group, following by reaction of the resulting free amine with a compound of formula 1 as described above then provides a compound of Formula (I).

10 Other compounds of Formula (I) can be prepared by methods disclosed in US and PCT Applications publication Nos. 2003/0092634A1, WO 02/098850 and WO 03/024924, US Patent Nos. 6,506,733 the disclosures of which are incorporated herein by reference in their entirety.

Other methods for preparing compounds of Formula (I) are described in US Patents 6,576,630 and PCT application publication No. WO 00/55126 the disclosures of which are 15 incorporated herein by reference in their entirety.

Compounds of Formula (I) where E is a group of formula (a) can be prepared by methods disclosed in PCT Application Publication No. 03/037892 which is incorporated herein by reference in its entirety.

Compounds of Formula (I) where E is  $-C(R^5)(R^6)X^1$  where  $X^1$  is -CHO, 20  $-C(R^7)(R^8)CF_3$ ,  $-C(R^7)(R^8)CF_2CF_2R^9$ ,  $-C(R^7)(R^8)C(R^7)(R^8)R^{10}$ ,  $-C(R^7)(R^8)CF_2C(O)NR^{10}R^{11}$ , or  $-C(R^7)(R^8)C(O)NR^{10}R^{11}$  can be prepared by methods disclosed in PCT Application Publication No. 95/09838 which is incorporated herein by reference in its entirety.

Compounds of Formula (I) where E is  $-C(R^5)(R^6)X^1$  where  $X^1$  is  $-C(R^7)(R^8)CH_2OR^{10}$  can be prepared by the methods described in US Patent 6,506,733 which is incorporated herein by 25 reference in its entirety.

#### Additional Processes for Preparing Compounds of Formula (I):

A compound of the present invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition 30 salt of a compound of the present invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds

of the present invention are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of the present invention can be prepared using salts of the starting materials or intermediates.

5 The free acid or free base forms of the compounds of the present invention can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of the present invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the present invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

10 The *N*-oxides of the compounds of the present invention can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of the present invention with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as 15 dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of the present invention can be prepared from the *N*-oxide of an appropriate starting material.

20 Compounds of the present invention in unoxidized form can be prepared from *N*-oxides of compounds of the present invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

25 Prodrug derivatives of the compounds of the present invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the present invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

30 Protected derivatives of the compounds of the present invention can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3<sup>rd</sup> edition, John Wiley & Sons, Inc. 1999.

Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

5 Compounds of the present invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diasteromeric derivatives of compounds of the present invention, dissociable complexes are preferred (e.g., 10 crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that 15 would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

20 Preparation of Biological Agents

In practicing this invention several processes for the generation or purification of biological agents are used. Methods for preparing the biologics are well known in the art as discussed below.

25 Monoclonal antibodies are prepared using standard techniques, well known in the art, such as by the method of Kohler and Milstein, *Nature* 1975, 256:495, or a modification thereof, such as described by Buck et al. 1982, *In Vitro* 18:377. Typically, a mouse or rat is immunized with the MenB PS derivative conjugated to a protein carrier, boosted and the spleen (and optionally several large lymph nodes) removed and dissociated into single cells. If desired, the spleen cells may be 30 screened (after removal of non-specifically adherent cells) by applying a cell suspension to a plate or well coated with the antigen. B-cells, expressing membrane-bound immunoglobulin specific for the antigen, will bind to the plate, and will not be rinsed away with the rest of the suspension. Resulting B-cells, or all dissociated spleen cells, are then induced to fuse with myeloma cells to

form hybridomas. Representative murine myeloma lines for use in the hybridizations include those available from the American Type Culture Collection (ATCC).

Chimeric antibodies composed of human and non-human amino acid sequences may be formed from the mouse monoclonal antibody molecules to reduce their immunogenicity in  
5 humans (Winter et al. *Nature* 1991 349:293; Lobuglio et al. *Proc. Nat. Acad. Sci. USA* 1989 86:4220; Shaw et al. *J. Immunol.* 1987 138:4534; and Brown et al. *Cancer Res.* 1987 47:3577; Riechmann et al. *Nature* 1988 332:323; Verhoeyen et al. *Science* 1988 239:1534; and Jones et al. *Nature* 1986 321:522; EP Publication No.519,596, published Dec. 23, 1992; and U.K. Patent Publication No. GB 2,276,169, published Sep. 21, 1994).

10 Antibody molecule fragments, e.g., F(ab')<sub>n</sub>.sub.2, FV, and sFv molecules, that are capable of exhibiting immunological binding properties of the parent monoclonal antibody molecule can be produced using known techniques. Inbar et al. *Proc. Nat. Acad. Sci. USA* 1972 69:2659; Hochman et al. *Biochem.* 1976 15:2706; Ehrlich et al. *Biochem.* 1980 19:4091; Huston et al. *Proc. Nat. Acad. Sci. USA* 1988 85(16):5879; and U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et  
15 al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

In the alternative, a phage-display system can be used to expand the monoclonal antibody molecule populations *in vitro*. Saiki, et al. *Nature* 1986 324:163; Scharf et al. *Science* 1986 233:1076; U.S. Pat. Nos. 4,683,195 and 4,683,202; Yang et al. *J. Mol. Biol.* 1995 254:392; Barbas, III et al. *Methods: Comp. Meth Enzymol.* 1995 8:94; Barbas, III et al. *Proc. Natl. Acad. Sci. USA* 1991 88:7978.

20 The coding sequences for the heavy and light chain portions of the Fab molecules selected from the phage display library can be isolated or synthesized, and cloned into any suitable vector or replicon for expression. Any suitable expression system can be used, including, for example, bacterial, yeast, insect, amphibian and mammalian systems. Expression systems in bacteria include those described in Chang et al. *Nature* 1978 275:615, Goeddel et al. *Nature* 1979 281:544, Goeddel et al. *Nucleic Acids Res.* 1980 8:4057, European Application No. EP 36,776, U.S. Pat. No. 4,551,433, deBoer et al. *Proc. Natl. Acad. Sci. USA* 1983 80:21-25, and Siebenlist et al. *Cell* 1980 20:269.

25 Expression systems in yeast include those described in Hinnen et al. *Proc. Natl. Acad. Sci. USA* 1978 75:1929, Ito et al. *J. Bacteriol.* 1983 153:163, Kurtz et al. *Mol. Cell. Biol.* 1986 6:142, Kunze et al. *J. Basic Microbiol.* 1985 25:141, Gleeson et al. *J. Gen. Microbiol.* 1986 132:3459, Roggenkamp et al. *Mol. Gen. Genet.* 1986 202:302, Das et al. *J. Bacteriol.* 1984 158:1165, De

1 Louvencourt et al. *J. Bacteriol.* 1983 154:737, Van den Berg et al. *Bio/Technology* 1990 8:135, Kunze et al. *J. Basic Microbiol.* 1985 25:141, Cregg et al. *Mol. Cell. Biol.* 1985 5:3376, U.S. Pat. Nos. 4,837,148 and 4,929,555, Beach et al. *Nature* 1981 300:706, Davidow et al. *Curr. Genet.* 1985 10:380, Gaillardin et al. *Curr. Genet.* 1985 10:49, Ballance et al. *Biochem. Biophys. Res. Commun.* 1983 112:284-289, Tilburn et al. *Gene* 1983 26:205-221, Yelton et al. *Proc. Natl. Acad. Sci. USA* 1984 81:1470-1474, Kelly et al. *EMBO J.* 1985 4:475479; European Application No. EP 244,234, and International Publication No. WO 91/00357.

2 Expression of heterologous genes in insects can be accomplished as described in U.S. Pat. No. 4,745,051, European Application Nos. EP 127,839 and EP 155,476, Vlak et al. *J. Gen. Virol.* 1988 69:765-776, Miller et al. *Ann. Rev. Microbiol.* 1988 42:177, Carbonell et al. *Gene* 1988 73:409, Maeda et al. *Nature* 1985 315:592-594, Lebacq-Verheyden et al. *Mol. Cell. Biol.* 1988 8:3129, Smith et al. *Proc. Natl. Acad. Sci. USA* 1985 82:8404, Miyajima et al. *Gene* 1987 58:273, and Martin et al. *DNA* 1988 7:99. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts are described in Luckow et al. *Bio/Technology* 1988 6:47-55, Miller et al. *GENERIC ENGINEERING*, Setlow, J. K. et al. eds., Vol. 8, Plenum Publishing, pp. 1986 277-279, and Maeda et al. *Nature* 1985 315:592-594.

3 Mammalian expression can be accomplished as described in Dijkema et al. *EMBO J.* 1985 4:761, Gorman et al. *Proc. Natl. Acad. Sci. USA* 1982 79:6777, Boshart et al. *Cell* 1985 41:521, and U.S. Pat. No. 4,399,216. Other features of mammalian expression can be facilitated as described in Ham et al. *Meth. Enz.* 1979 58:44, Barnes et al. *Anal. Biochem.* 1980 102:255, U.S. Pat. Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655 and Reissued U.S. Pat. No. RE 30,985, and in International Publication Nos. WO 90/103430, WO 87/00195.

4 The production of recombinant adenoviral vectors are described in U.S. Pat. No. 6,485,958.

5 Botulinum toxin type A can be obtained by establishing and growing cultures of *Clostridium botulinum* in a fermenter and then harvesting and purifying the fermented mixture in accordance with known procedures.

6 Any of the above-described protein production methods can be used to provide the biologic that would benefit from the present invention.

30

#### Utility

7 The compounds of the invention are selective inhibitors of cysteine proteases, in particular,

cathepsin S, K, B, and/or F, and accordingly are useful for treating diseases in which cysteine protease activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention are useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, psoriasis, multiple sclerosis, pemphigus vulgaris, Graves'

5 disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders, including, but not limited to, asthma, allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts and endometriosis.

Cathepsin S is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in 10 asthma and bronchitis, pneumonitis and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

#### Testing

15 The cysteine protease inhibitory activity, in particular, the Cathepsin S inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease-induced hydrolysis of a peptide-based substrate. Details of assays for measuring protease inhibitory activity are set forth in

20 Biological Examples 1-6, *infra*.

#### Administration and Pharmaceutical Compositions

In general, a compound of the present invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in 25 combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of compounds of the present invention may range from about 10 micrograms per kilogram body weight ( $\mu\text{g}/\text{kg}$ ) per day to about 20 milligram per kilogram body weight (mg/kg) 30 per day, typically from about 100  $\mu\text{g}/\text{kg}/\text{day}$  to about 10 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 1 mg/day to about 1.6 g/day, typically from about 1 mg/day to about 100 mg/day. In general, one of ordinary skill in the art,

acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of the present invention for treating a given disease.

The compounds of the present invention can be administered as pharmaceutical

5 compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of the present invention in combination with at least one  
10 pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, 15 gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include  
20 water, saline, aqueous dextrose and glycols.

The amount of a compound of the present invention in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of the present invention for treating a given disease will comprise from 0.01%w to  
25 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of the present invention are described in working example below.

30

### EXAMPLES

The following preparations and examples are given to enable those skilled in the art to

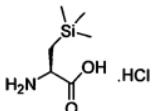
more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

### Synthetic Examples

5

#### Reference A

##### Synthesis of (*R*)-2-amino-3-trimethylsilylpropionic acid



##### Step 1

To a stirred solution of the 3-(trimethylsilyl)propionic acid (10 g, 68.5 mmol) in THF (100 ml) was added oxalyl chloride (8.9 ml, 102.7 mmol) and a drop of DMF at room temperature. After stirring for 2 h, the solvent and excess of oxalyl chloride was removed under vacuum. The product 3-trimethylsilylpropionyl chloride was used in the next step without further purification.

##### Step 2

To a stirred solution of (*S*)-4-benzyl-2-oxazolidinone (12.1 g, 68.5 mmol) in THF (100 ml) was added *n*-BuLi (1.6 M solution in hexane, 42.8 ml, 68.5 mmol) at -75° C. After stirring for 30 min., 3-trimethylsilylpropionyl chloride was added and the reaction mixture was allowed to warm to room temperature and then quenched with saturated NH4Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO4 and concentrated. The residue was purified by silica gel column chromatography to yield (*S*)-4-benzyl-3-[3-(trimethylsilyl)propionyl]oxazolidin-2-one (16.15g).

##### Step 3

Sodium azide (21.45 g, 0.33 mol) was dissolved in water-ethanol (300 ml, 1:1) and 2,4,6-triisopropylbenzenesulfonyl chloride (30.3 g, 0.1 mol) was added at room temperature. After stirred for 14 h, the reaction mixture was diluted with water and then extracted with ethyl ether. The organic layer was washed with brine, dried with MgSO4, and the solvent was removed under vacuum. Methanol (50 ml) was added to the residue to give 2,4,6-triisopropylbenzenesulfonyl azide as a white crystalline solid (27.5g).

##### Step 4

In to a solution of (*S*)-4-benzyl-3-[3-(trimethylsilyl)propionyl]-oxazolidin-2-one (6.1 g, 20 mmol) in THF (50 ml) was added potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 44 ml, 22 mmol) at -65° C. After stirring for 2 h, 2,4,6-triisopropylbenzenesulfonyl azide (7.4 g, 24 mmol) in THF (50 ml) was added at -75° C. After stirring for 20 min., acetic acid (3 g) was added and the reaction mixture was allowed to warm to room temperature. 1N hydrochloric acid (11.2 ml) was added and the product was extracted with ethyl acetate. The organic layer was collected and washed with brine and dried with MgSO<sub>4</sub>. The organics were removed to give a residue which was purified by silica gel column chromatography to yield (2*R*, 4*S*)-4-benzyl-3-[3-(trimethylsilyl)-2-azidopropionyl]oxazolidin-2-one (3.2 g).

**10 Alternate synthesis:**

Tetrahydrofuran (120 ml) was cooled to -70° C and then treated with potassium hexamethyldisilazide (0.5 M, 80 ml). A precooled solution of (*S*)-4-benzyl-3-[3-(trimethylsilyl)propionyl]-oxazolidin-2-one (10.6 g) in THF (120 ml) was added at -66° C over 15 min. A solution of 2,4,6-triisopropylbenzenesulfonyl azide (13.7 g) in tetrahydrofuran (120 ml) was added over 10 min. After 5 min., a solution of acetic acid (9 ml) in tetrahydrofuran (10 ml) was added and the reaction mixture warmed to 25° C. The reaction mixture was diluted with water, treated with sodium chloride and then extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and evaporated in vacuo. Chromatography of the residue on silica gel eluting with ethyl acetate – hexane mixtures gave (2*R*, 4*S*)-4-benzyl-3-[3-(trimethylsilyl)-2-azidopropionyl]oxazolidin-2-one as a colorless oil (9.06 g).

**20 Step 5**

(2*R*, 4*S*)-4-Benzyl-3-[3-(trimethylsilyl)-2-azidopropionyl]oxazolidin-2-one was dissolved in tetrahydrofuran (400 ml) and cooled to 0° C and then treated with a solution of lithium hydroxide (1.09 g), water (140 ml), and 30% hydrogen peroxide (13.3 ml) over 35 min. 25 After 75 min., a solution of sodium hydrogen sulfite (31 g) in water (140 ml) was added over 25 min. The tetrahydrofuran was removed by rotary evaporation and the product was isolated by extraction with ethyl acetate. Purification by silica gel chromatography eluting with ethyl acetate – hexane then gave (2*R*)-azido-3-trimethylsilylpropionic acid (4.36 g).

**30 Step 6**

(2*R*)-Azido-3-trimethylsilylpropionic acid (2.38 g) in methanol (120 ml) was treated with 10% Pd/C (130 mg) and hydrogenated at 48 psi for 1 h. The catalyst was removed by filtration

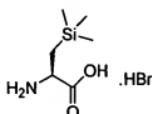
through celite. Evaporation of the methanol then gave (*R*)-2-amino-3-trimethylsilylpropionic acid (1.50 g) as a white solid

LC-MS: 159.7(M-1); 161.7(M+1); 184(M+Na).

5

### Reference B

#### Synthesis of (*R*)-2-amino-3-trimethylsilylpropionic acid hydrobromide



#### Step 1

(a) To a stirred solution of benzyloxycarbonyl- $\alpha$ -phosphonoglycine trimethyl ester (16.6 g, 50 mmol) in dichloromethane (50 ml) at room temperature was added DBU (8.4 g, 55 mmol). After stirring for 30 min., the reaction mixture was added to the following reaction mixture.

(b) To a stirred solution of oxalyl chloride (9.2 g, 72 mmol) in dichloromethane (150 ml) at -78 °C was added dimethyl sulfoxide (6.4 g, 82 mmol). After 15 min., a solution of trimethylsilylmethanol (5 g, 48 mmol) in dichloromethane (30 ml) was added over 10 min. to the reaction mixture. After 30 min., triethylamine (17.94 g, 177.6 mmol) was added. After 30 min., the reaction mixture prepared in (a) was added at -78 °C. After stirring for 15 min., the reaction mixture was allowed to warm up to room temperature and then quenched with 1N HCl. The organics were removed on roto-evaporator and the residue was extracted with ethyl ether. The organic layer was separated and washed with brine, dried with MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography to yield (*Z*)-2-benzyloxycarbonyl-amino-3-(trimethylsilyl)acrylic acid methyl ester (5.1 g).

#### Step 2

To a solution of (*Z*)-2-benzyloxycarbonylamino-3-(trimethylsilyl)-acrylic acid methyl ester (150 mg, 0.49 mmol) in ethyl acetate (3 ml) was added (+)-1,2-bis-(2S,5S)-2,5-diethylphospholobenzene(cyclooctadiene) rhodium(I) trifluoromethansulfonate (7mg, 0.0098mmol). The reaction mixture was stirred under hydrogen atmosphere at 5 psi for 2 h. Ethyl acetate was removed and the residue was purified by silica gel column chromatography to yield (*R*)-2-benzyloxycarbonylamino-3-(trimethylsilyl)-propionic acid methyl ester (150 mg).

e.e (>98%) was determined by analytical chiral column HPLC (Column: OD, solvent: 90% hexane, 10% isopropanol and 1ml/min.).

Step 3

To a stirred solution of (*R*)-2-benzyloxycarbonylamino-3-(trimethylsilyl)propionic acid 5 methyl ester (4.2 g, 13.6 mmol) in methanol (30 ml) was added 1N NaOH solution (20 ml) at room temperature. After stirring for 2 h, the reaction mixture was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO<sub>4</sub> and concentrated to give (*R*)-2-benzyloxycarbonylamino-3-(trimethylsilyl)propionic acid (4 g).

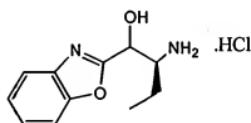
Step 4

10 To a stirred flask contain (*R*)-2-benzyloxycarbonylamino-3-(trimethylsilyl)propionic acid (4 g, 13.5 mmol) was added hydrogen bromide 33wt% solution in acetic acid (10 ml). After stirring for 2 h, the access hydrogen bromide and acetic acid were removed under vacuum. Ethyl ether (40 ml) was added to the residue and after stirring for 30 min. the solid was filtered, washed with ethyl ether, and dried to give (*R*)-2-amino-3-(trimethylsilyl)propionic acid hydrogen 15 bromide (3.2 g).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.11 (3H, s), 3.82 (1H, t), 1.05 (2H, dd), 0.06 (9H, s). LC-MS: 160.1 (M-1); 161.8 (M+1).

Reference C

20 Synthesis of (*S*)-2-amino-1-benzoxazol-2-ylbutan-1-ol hydrochloride



Step 1

To a solution of benzoxazole (28.6 g, 240 mmol) in toluene (150 ml) was added during ca 20 min., at about -4 °C a 2 M solution of isopropyl-magnesium chloride in THF (120 ml, 240 25 mmol). The red-brown mixture was stored at ca -4°C and used as needed.

Step 2

To a solution of (*S*)-2-Boc-aminobutanol (50 g; 264 mmol) in dichloromethane (500 ml) and water (350 ml) were added at 20° C TEMPO (0.01 eq), sodium bromide (1 eq) and sodium hydrogencarbonate (3 eq). The reaction mixture was stirred at 0° C and diluted bleach (1.3 eq,

450 ml) was added over 40 min. The reaction mixture was stirred for 30 min. at 0° C and then quenched with aq. thiosulfate. After decantation and extractions (dichloromethane), the organic phase was washed with brine, dried and concentrated *in vacuo* to dryness, giving (*S*)-2-(*tert*-butoxycarbonyl)-aminobutyraldehyde as a low-melting solid (38.1 g; yield: 77%).

5 Step 3

A solution of (*S*)-2-(*tert*-butoxycarbonyl)amino-butyraldehyde (30 g, 160 mmol) in toluene (150 ml) was added over 30 min. at -5° C to a solution of Grignard reagent of benzoxazole (prepared as described in Step 1 above). The reaction mixture was stirred for 0.5 h at 0° C, then 2.5 h at RT. Quenching with 5% aq. acetic acid, washings with 5% aq. sodium carbonate, then brine and concentration to dryness gave crude (*S*)-2-(*tert*-butoxycarbonyl)-amino-1-benzoxazol-2-yl-butan-1-ol. The residue was diluted with toluene, and silica gel was added. The slurry was filtered. Elution by toluene removed the non-polar impurities. Then an 8/2 mixture of toluene and ethyl acetate desorbed the (*S*)-2-(*tert*-butoxycarbonyl)-amino-1-benzoxazol-2-ylbutan-1-ol.

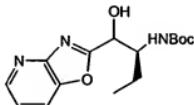
10 Step 4

To a solution of (*S*)-2-(*tert*-butoxycarbonyl)amino-1-benzoxazol-2-yl-propan-1-ol (26.3 g, 86 mmol) in isopropanol (118 ml) at 20-25 °C was added trimethylchlorosilane (1.4 eq). The solution was stirred for 5 h at 50° C. Concentration of the reaction mixture to 52 ml followed by addition of isopropyl ether (210 ml), filtration and drying under vacuum afforded

20 (*S*)-2-amino-1-benzoxazol-2-ylbutan-1-ol hydrochloride salt as a grey solid (16.4 g; yield = 79 %; mixture of diastereomers).

#### Reference D

Synthesis of 2(*S*)-(*tert*-butoxycarbonyl)amino-1-(oxazolo[4,5-*b*]pyridin-2-yl)butan-1-ol



25

Step 1

A mixture of 2-amino-3-hydroxypyridine (11 g, 100 mmol), triethylorthoformate (80 ml) and p-toluenesulfonic acid (61 mg) was heated at 140 °C for 8 h. Excess triethylorthoformate was removed under vacuum and oxazolo[4,5-*b*]pyridine was crystallized from ethyl acetate (9 g).

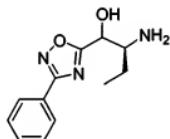
30 Step 2

In a clean roundbottom flask equipped with stir bar was placed oxazolo[4,5-b]pyridine (600 mg, 5 mmol) in THF (30 ml) and the reaction mixture was cooled to 0 °C under N<sub>2</sub> atmosphere. Isopropylmagnesium chloride (2 M in THF, 2.5 ml, 5 mmol) was added. After stirring for 1 h at 0 °C, (S)-2-(*tert*-butoxycarbonyl)aminobutyraldehyde ( 573 mg, 3 mmol) in 5 THF (20 ml) was added. The ice bath was removed and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was quenched with saturated ammonium chloride solution and concentrated to dryness. The residue was extracted with EtOAc, then washed with brine, dried with anhyd. MgSO<sub>4</sub>, filtered and concentrated. The crude product was purified by chromatograph to yield 383 mg of the desired compound.

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.42 (m, 1H), 8.18 (m, 1H), 7.3(m, 1H), 6.8- 6.6 (dd, d, 1H, OH, diastereomer), 6.3- 6.02 (d, d, 1H, NH, diastereomer), 4.82- 4.5 (m,m, 1H, diastereomer), 1.8-1.3 (m, 2H), 1.2-1.05 (s,s, 9H, diastereomer), 0.89 (m, 3H). MS: 306.2 (M-1), 308.6 (M+1).

#### Reference E

15 Synthesis of (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol



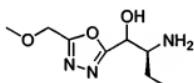
20 3-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid (500 mg, 2.14 mmol) was combined with EDC (600 mg, 3.14 mmol), HOBt (600 mg, 3.92 mmol), and *N*-hydroxybenzamidine (292 mg, 2.14 mmol). Dichloromethane (10 ml) was added and then 4-methylmorpholine (1 ml). The reaction mixture was stirred at ambient temperature for 16 h. After dilution with ethyl acetate (200 ml), the solution was washed with water (30 ml), saturated aqueous NaHCO<sub>3</sub> solution and brine, dried with MgSO<sub>4</sub> and evaporated under vacuum. The crude 25 product was dissolved in pyridine (10 ml) and heated at 80 °C for 15 h. The pyridine was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (eluent: ethyl acetate) to yield (290mg, 0.83 mmol) of (S)-2-*tert*-butoxycarbonylamino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol. (S)-2-*tert*-butoxycarbonylamino-1-(3-phenyl-

[1,2,4]oxadiazol-5-yl)-butan-1-ol (145 mg, 0.41 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 ml) and TFA (4 ml) was added. After stirring for 1 h, the reaction mixture was evaporated to dryness to yield (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol.

Following the procedure described above but substituting *N*-hydroxypropamidine for *N*-hydroxy-benzamidine provided (S)-2-amino-1-(3-ethyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol.

#### Reference F

##### Synthesis of (S)-2-amino-1-(2-methoxymethyl-[1,3,4]oxadiazol-5-yl)butan-1-ol



10

##### Step 1

(S)-(+)-2-amino-1-butanol (50 g, 561 mmol) in a mixture of water and dioxane (200 ml of water and 200 ml dioxane) was cooled to 0 °C and mixed with NaOH (26.9 g, 673 mmol) and *tert*-butyl-dicarbonate (146.96 g, 673 mmol). After the addition, the reaction was allowed to warm to room temperature. The reaction mixture was stirred for 2 h. After removing the dioxane, the residue was extracted with EtOAc, then washed with brine and dried with anhydrous  $\text{MgSO}_4$ , filtered and concentrated. Without further purification, the crude (S)-2-Boc-amino-1-butanol (120 g) was used for next step reaction.

##### Step 2

20 A solution of oxalyl chloride (40.39 g, 265 mmol) in  $\text{MeCl}_2$  (700 ml) was stirred and cooled to -60 °C. Dimethylsulfoxide (51.7 g, 663 mmol) in  $\text{MeCl}_2$  (100 ml) was added dropwise. After 10 min., a solution of (S)-2-Boc-amino-1-butanol (50 g, 265 mmol) in  $\text{MeCl}_2$  (100 ml) was added dropwise at -70 °C. The reaction mixture was allowed to warm to -40 °C for 10 min. and then cooled to -70 °C again. A solution of triethylamine (74.9 g, 742 mmol) in  $\text{MeCl}_2$  (100 ml) was added. The reaction mixture was allowed to warm to room temperature over 2 h. Saturated sodium dihydrogen phosphate (100 ml) was added, and then the organic layer was washed with brine and dried over  $\text{MgSO}_4$ . The solvent was removed to yield 45g of (S)-2-Boc-amino-butyraldehyde(1-formyl-propyl)-carbamic acid *tert*-butyl ester.

##### Step 3

A mixture of methyl methoxyacetate (52 g, 500 mmol), hydrazine hydrate (30 ml) was heated to reflux for 8 h. Excess hydrazine and water were removed under vacuum. The residue was extracted with n-butanol, dried with Na<sub>2</sub>SO<sub>4</sub>. Excess n-butanol was removed to yield 45g of hydrazide.

5 Step 4

A mixture of above hydrazide (45 g), triethylorthoformate (146 ml) and p-toluenesulfonic acid (61mg) was heated at 140 °C for 8 h. Excess triethylorthoformate was removed under vacuum. The product was purified by silica gel column chromatography to yield 4.6g of 2-methoxymethyl-1,3,4-oxadiazole.

10 Step 5

To a stirred solution of 2-methoxymethyl-1,3,4-oxadiazole (4.6 g, 40 mmol) in THF (100 ml) was added *n*-BuLi (1.6 M solution in 25.2 ml of hexane) dropwise under N<sub>2</sub> at -78 °C. After 1 h, MgBr.Et<sub>2</sub>O (10.4 g, 40.3 mmol) was added and the reaction mixture was allowed to warm to -45 °C for 1 h before being treated with (S)-2-Boc-amino-propenylaldehyde butyraldehyde (5.28 g,

15 28.25 mmol) in THF (20 ml). The reaction mixture was stirred for 1 h, quenched with saturated NH<sub>4</sub>Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography to yield (S)-2-Boc-amino-1-(5-methoxymethyl-[1,3,4]-oxadiazole-2-yl)-1-propanol butanol (500 mg).

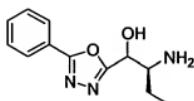
Step 6

20 2-Boc-amino-1-(5-methoxymethyl-[1,3,4]-oxadiazole-2-yl)-1-propanol butanol (500 mg, 1.66 mmol), and MeCl<sub>2</sub> (5 ml) were mixed and TFA (0.5 ml) was added at room temperature. After stirring for 1 h, the solvent and excess TFA were removed under vacuum to produce (S)-2-amino-1-(5-methoxymethyl-[1,3,4]oxadiazol-2-yl)-butan-1-ol. TFA salt (340 mg).

25

Reference G

Synthesis of (S)-2-amino-1-(2-phenyl-[1,3,4]oxadiazol-5-yl)-1-butan-1-ol



Step 1

A mixture of the benzoic hydrazide (22.5 g, 165 mmol), triethylorthoformate (150 ml) and p-toluenesulfonic acid (300 mg) was heated at 120 °C for 12 h. Excess triethylorthoformate was removed under vacuum and the residue was purified by silica gel column chromatography to produce 2-phenyl-[1,3,4]-oxadiazole (14.5 g).

5 Step 2

To a stirred solution of the 2-phenyl-[1,3,4]oxadiazole (10 g, 68.5 mmol) in THF (100 ml) was added *n*-BuLi (1.6 M solution in 42.8 ml of hexane) dropwise under N<sub>2</sub> at -78 °C. After 1 h, MgBr.Et<sub>2</sub>O (17.69 g, 68.5 mmol) was added and the reaction mixture was allowed to warm to -45 °C for 1 h before being treated with (S)-2-*Boc*-aminobutrya-aldehyde (7.8 g, 41 mmol) in THF (20 ml). The reaction mixture was stirred for 1 h, quenched with saturated NH<sub>4</sub>Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography to yield 2-((S)-2-*Boc*-amino-1-hydroxybutyl)-5-phenyl-[1,3,4]-oxadiazole (9.7 g).

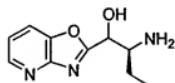
Step 3

15 2-((S)-2-*Boc*-amino-1-hydroxybutyl)-5-phenyl-[1,3,4]-oxadiazole (505 mg, 1.5 mmol) and MeCl<sub>2</sub> (5 ml) were mixed and TFA (1 ml) was added at room temperature. After stirring for 1 h, the solvent and excess TFA were removed under vacuum to produce 530 mg of (S)-2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-butanol TFA salt.

20

Reference H

Synthesis of (S)-2-amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol



Step 1

25 A mixture of 2-amino-3-hydroxypyridine (25 g, 227 mmol), triethylorthoformate (75 ml) and p-toluenesulfonic acid (61 mg) was heated at 140 °C for 8 h. Excess triethylorthoformate was removed under vacuum. The product was crystallized from ethyl acetate to yield 22.5 g of oxazolo[4,5-b]pyridine.

Step 2

To a stirred solution of the oxazolo[4,5-b]pyridine (12 g, 100 mmol) in THF (300 ml) was added *n*-BuLi (1.6 M solution in 62.5 ml of hexane) drop wise under N<sub>2</sub> at -78 °C. After 1 h, MgBr·Et<sub>2</sub>O (25.8 g, 100 mmol) was added and the reaction mixture was allowed to warm to -45 °C for 1 h before being treated with (S)-2-*Boc*-amino-butylaldehyde (11.46 g, 60 mmol) in THF (50 ml). The reaction mixture was stirred for 1 h, quenched with saturated NH<sub>4</sub>Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography to yield (S)-2-*Boc*-amino-1-(oxazolo[4,5-b]pyridin-2-yl)-1-butanol (14.1 g).

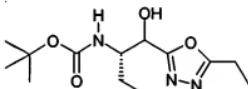
10 Step 3

(S)-2-*Boc*-amino-1-(oxazolo[4,5-b]pyridin-2-yl)-1-butanol (311 mg, 1 mmol) and MeCl<sub>2</sub> (5mL) were mixed and TFA (1mL) was added at room temperature. After stirring for 1 h, the solvent and excess TFA were removed under vacuum to produce 355 mg of (S)-2-amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol. TFA salt.

15

Reference I

Synthesis of {1-[(2-ethyl-1,3,4]oxadiazol-2-yl)hydroxymethyl]propyl}carbamic acid *tert*-butyl ester



20

Step 1

A mixture of the formic hydrazide (60 g, 1 mole), triethylorthopropionate (176.26 g, 1 mole) and *p*-toluenesulfonic acid (250 mg) was heated at 120° C for 12 hours. The ethanol was removed under vacuum and the residue was distilled under vacuum to yield 24g of ethyl-1,3,4-oxadiazole.

25

Step 2

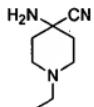
To a stirred solution of the ethyl-1,3,4-oxadiazole (4.66 g, 48 mmol) in THF (50 ml) was added *n*-BuLi (1.6M solution in 30 ml of hexane) drop-wise under N<sub>2</sub> at -78°C. After 1 hour, MgBr·Et<sub>2</sub>O (12.38 g, 48 mmol) was added and the reaction mixture was allowed to warm to -45° C for 1 hour before being treated with 2-*Boc*-Nlu-aldehyde (3.2 g, 24 mmol) in THF (20 ml). The reaction mixture was stirred for 1 hour, quenched with saturated NH<sub>4</sub>Cl, and extracted with ethyl

acetate. The organic layer was washed with brine, dried with  $\text{MgSO}_4$  and concentrated. The residue was purified by silica gel column chromatography to yield {1-[(2-ethyl-[1,3,4]oxadiazol-5-yl)hydroxymethyl]propyl}carbamic acid *tert*-butyl ester (2.13g).  $^1\text{H}$  NMR (DMSO- $\delta$ ): 6.65-6.52 (1H, d, d,  $J$ =9.2Hz,  $J$ =9.2Hz, NH, diastereomer), 6.14, 5.95 (1H, d, d,  $J$ =5.6Hz,  $J$ =5.6Hz, OH, 5 diastereomer), 4.758- 4.467 (1H, m, diastereomer), 3.7-3.55 (1H, m), 2.8 (2H, q), 1.33(12H, t), 1.25-1.21 (2H, m), 0.82 (3H, m). MS: 284.1 (M-1), 286 (M+1), 308 (M+Na).

#### Reference J

##### Synthesis of 4-amino-4-cyano-1-ethylpiperidine

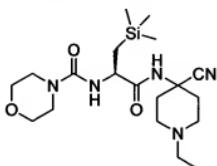
10



A mixture of 1-ethyl-4-piperidone (13.2 ml, 100 mmol), ammonium chloride (21.4 g, 400 mmol), sodium cyanide (19.6 g, 400 mmol) and water (550 ml) was stirred at room temperature 15 for 48 h. The pH of the reaction mixture was adjusted to 10.1 and the product was extracted with ethyl acetate. The organic extracts were washed with brine and dried over magnesium sulfate. Rotary evaporation of the solvent gave a mixture of 4-amino-4-cyano-1-ethyl piperazine and 4-hydroxy-4-cyano-1-ethyl piperazine (7.67 g). This mixture of products was treated with 7 M ammonia in methanol (20 ml) and allowed to stand at room temperature for 24 h. The methanol 20 and excess ammonia were removed *in vacuo* and the residue was cooled to give 4-amino-4-cyano-1-ethylpiperidine as a crystalline solid (7.762 g).

#### Example 1

##### Synthesis of (1*R*)-morpholine-4-carboxylic acid [1-(4-cyano-1-ethylpiperidin-4-ylcarbamoyl)-2-(trimethylsilyl)ethyl]amide



Step 1

A mixture of (*R*)-2-amino-3-trimethylsilylpropionic acid (0.320 g) and *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) (1.85 g) was heated at 70° C for 60 min. The reaction mixture was cooled and the excess MSTFA was removed *in vacuo*. Morphinocarbonyl chloride (0.70 ml) was added to the reaction mixture which was heated at 70° C for 45 min. and then cooled. Water and ice (25 ml) was added to the reaction mixture which was stirred until the evolution of carbon dioxide ceased. The solution was extracted with ethyl acetate to give (*2R*)-[(morpholine-4-carbonyl)amino]-3-(trimethylsilyl)-propionic acid (0.529 g) which was used in the following step without further purification.

Step 2

To a solution of (*2R*)-2-[(morpholine-4-carbonyl)amino]-3-(trimethylsilyl)propionic acid (140 mg, 0.51 mmol) in DMF (2ml) was added 4-amino-4-cyano-1-ethylpiperidine hydrochloride salt (99 mg, 0.52 mmol), HATU (296 mg, 0.78 mmol) and diisopropylethylamine (198 mg, 1.53 mmol) at room temperature. After 2 h, the reaction mixture was extracted with ethyl acetate, washed with brine, and dried. After removing the solvent, the residue was purified by silica gel column chromatography to yield the title compound (87 mg).

$^1\text{H}$  NMR (DMSO- $\text{d}_6$ ):  $\delta$  8.24 (1H, s), 6.5 (1H, d,  $J=8.8\text{Hz}$ ), 4.18 (1H, m), 3.6-3.48 (4H, m), 3.35-3.2 (4H, m), 2.75-2.55 (2H, m), 2.32 (2H, q,  $J=7.2\text{Hz}$ ), 2.3-2.1 (4H, m), 1.9-1.7 (2H, m), 0.98 (3H, t,  $J=7.2\text{Hz}$ ), 1.1-0.8 (2H, m), 0.009 (9H, s). MS: 408.4(M-1), 410.3(M+1), 432.1 (M+Na).

Proceeding as described in Example 1 above but substituting 4-amino-4-cyano-1-ethylpiperidine hydrochloride salt with 1-aminocyclopropanecarbonitrile provided (1*R*)-morpholine-4-carboxylic acid [1-(1-cyanocyclopropylcarbamoyl)-2-(trimethylsilyl)ethyl]amide.

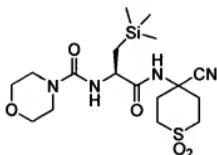
$^1\text{H}$  NMR (DMSO- $\text{d}_6$ ):  $\delta$  8.32 (1H, s), 8.04 (1H, s), 4.2 (1H, dd,  $J=7.2\text{Hz}$ ,  $J=14.4\text{Hz}$ ), 3.64 (4H, t,  $J=4.8\text{Hz}$ ), 3.31 (4H, m), 1.65-1.45 (2H, m), 1.25-1.15 (3H, m), 0.95-0.85 (1H, m), 0.008 (9H, s). MS: 337.3(M-1), 339(M+1), 361.1(M+Na).

Proceeding as described in Example 1 above but substituting 4-amino-4-cyano-1-ethylpiperidine hydrochloride salt with 1-aminotetrahydrothiopyran-4-ylcarbonitrile provide (1*R*)-morpholine-4-carboxylic acid [1-(4-cyanotetrahydrothiopyran-4-ylcarbamoyl)-2-(trimethylsilyl)ethyl]amide.

LC-MS: 397.1(M-1); 399.1(M+1); 421.3 (M+Na).

### Example 2

## Synthesis of (1*R*)-morpholine-4-carboxylic acid [1-(4-cyano-1,1-dioxohexahydro-1*λ*<sup>6</sup>-thiopyran-4-yl)carbamoyl]-2-(trimethylsilyl)ethyl]amide



5

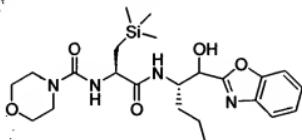
10 Into a solution of crude (1*R*)-morpholine-4-carboxylic acid [1-(4-cyanotetrahydrothiopyran-4-ylcarbamoyl)-2-(trimethylsilyl)ethyl]amide (260 mg, 0.51 mmol) in MeOH (15 ml) was added oxone (469 mg, 0.76 mmol) in water (15 ml) at room temperature. After 2 h, MeOH was removed under vacuum and the residue was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried, and concentrated. The residue was purified by silica gel column chromatography to yield the title compound (47 mg).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.39 (1H, s), 6.5 (1H, d, *J*=7.6Hz), 4.1 (1H, m), 3.49 (4H, t, *J*=4.4Hz), 3.4-3.1 (6H, m), 2.7-2.55 (2H, m), 2.5-2.4 (4H, m), 1.05-0.85 (2H, m), 0.008 (9H, s). MS: 429.2 (M-1), 431.1 (M+1), 453.2 (M+Na).

15

### Example 3

## Synthesis of morpholine-4-carboxylic acid {1(R)-[1(S)-(benzoxazol-2-ylhydroxymethyl)-butylcarbamoyl]-2-trimethylsilylanylethyl}amide



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Into a solution of (2*R*)-2-[(morpholine-4-carbonyl)amino]-3-(trimethylsilyl)propionic acid (140 mg, 0.51 mmol) in  $\text{CH}_2\text{Cl}_2$  (5ml) was added (2*S*)-2-amino-1-benzoazol-2-ylpentan-1-ol (121 mg, 0.55 mmol), HOBt (95 mg, 0.62 mmol), EDC (148 mg, 0.77 mmol) and NMM (154 mg, 1.53 mmol) at room temperature. After 2 h, the reaction mixture was extracted with ethyl

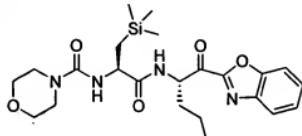
acetate and the organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography to yield the title compound (300 mg).

LC-MS: 475.4(M-1); 477.5(M+1); 499.5 (M+Na).

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#### Example 4

Synthesis of morpholine-4-carboxylic acid {1(R)-[1(S)-(benzoaxazol-2-ylcarbonyl)-butylcarbamoyl]-2-trimethylsilanylethyl} amide

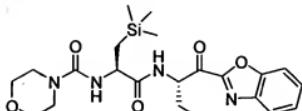


10 To a solution of crude morpholine-4-carboxylic acid {1(R)-[1(S)-(benzoaxazol-2-ylhydroxymethyl)-butylcarbamoyl]-2-trimethylsilanylethyl} amide (300 mg) from Example 3 above, in  $\text{MeCl}_2$  (5 ml) was added Dess-Martin periodinane (324 mg, 0.76 mmol) at room temperature. After stirring for 1 h, saturated  $\text{Na}_2\text{S}_2\text{O}_3\text{-NaHCO}_3$  (5 ml) were added. After a further 0.5 h, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with  $\text{MgSO}_4$  15 and concentrated. The residue was purified with silica gel column chromatography to yield the title compound (130mg).

20  $^1\text{H}$  NMR (DMSO- $\text{d}_6$ ):  $\delta$  8.37 (1H, d,  $J=6\text{Hz}$ ), 8.0 (1H, d,  $J=7.6\text{Hz}$ ), 7.9 (1H, d,  $J=8.4\text{Hz}$ ), 7.65 (1H, d,t,  $J=1.6\text{Hz}$ ,  $J=7.2\text{Hz}$ ), 7.55 (1H, d, t,  $J=1.2\text{Hz}$ ,  $J=7.6\text{Hz}$ ), 6.42 (1H, d,  $J=8.8\text{Hz}$ ), 6.21 (1H, m), 4.26 (1H, m), 3.51(4H, m), 3.35-3.2 (4H, m), 2.0-1.85 (1H, m), 1.8-1.65 (1H, m), 1.55-1.35(2H, m), 1-0.85 (5H, m), 0.008 (9H, s). MS: 473.3(M-1); 475.2(M+1); 497.3 (M+Na).

#### Example 5

Synthesis of morpholine-4-carboxylic acid {1(R)-[1(S)-(benzoaxazol-2-ylcarbonyl)-propylcarbamoyl]-2-trimethylsilanylethyl} amide



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#### Step 1

To a solution of (Z/E)-2-benzyloxycarbonylamino-3-(trimethylsilyl)acrylic acid methyl ester (Z/E=3:1, 43g, 140.1mmol) prepared as described in Reference B, Step 1 above, in ethyl acetate (100 ml) was added (+)-1,2-bis (2S,5S)-2,5-diethylphospholano benzene (cyclooctadiene) rhodium(I) trifluoromethansulfonate (500 mg, 0.692 mmol) under nitrogen atmosphere. Hydrogen gas was introduced at 20 psi. After 2 h, ethyl acetate was removed by rotary evaporation to yield crude (R)-2-benzyloxycarbonylamino-3-(trimethylsilyl)propionic acid methyl ester (43.8 g). Chiral HPLC analysis shows e.e >98%. (Column: OD, solvent: 90% hexane, 10% isopropanol and flow rate of 1ml/min. 20psi).

Step 2

To a stirred solution of (R)-2-benzyloxycarbonylamino-3-(trimethylsilyl)propionic acid methyl ester (43.8 g) in methanol (300 ml) was added 1N NaOH solution (170 ml) at 0 °C. After completion of the addition, the reaction was allowed to warm to room temperature. After stirring for 2 h at room temperature, HPLC showed the reaction was completed. Methanol was removed by rotary evaporation and the residue was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO<sub>4</sub> and concentrated to give crude (R)-2-benzyloxycarbonylamino-3-(trimethylsilyl)propionic acid (42.7 g).

Step 3

To a stirred flask contain (R)-2-benzyloxycarbonylamino-3-(trimethylsilyl)propionic acid. (42.7 g) was added hydrogen bromide in acetic acid (33 wt%, 90 ml). After stirring for 2 h, HPLC showed the starting material had been consumed. Ethyl ether (200 ml) was added and the reaction mixture was stirred for 30min. The precipitated product was filtered, washed with ethyl ether and dried to yield (R)-2-amino-3-(trimethylsilyl)propionic acid hydrogen bromide salt (22.5 g). The mother liquid was collected and the solvent was removed by rotary evaporation. The residue was stirred with mixture of a 1:1 mixture of ethyl ether and hexane (40 ml) to give additional 6 g of the product.

Step 4

A mixture of (R)-2-amino-3-(trimethylsilyl)propionic acid hydrobromide salt (1.439 g, 5.95 mmol) and *N*-methyl-*N*-trimethylsilyl trifluoroacetamide (MSTFA) (5.5 ml, 29.6 mmol) was heated at 69° C for 55 min. The *N*-methyltrifluoroacetamide and excess MSTFA were removed by rotary evaporation and the resulting residue was treated with morpholine carbonyl chloride (3.0 ml, 25 mmol) and heated again at 70° C for 40 min. After cooling, water (30 ml) and a little ice were added to the reaction mixture which was stirred at room temperature until the evolution of

CO<sub>2</sub> ceased (about 30 min). The reaction mixture was then extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated to give morpholine-4-carboxylic acid (1*R*)-2-trimethylsilanylethyl)amide (1.76 g) which was used in the next step without further purification.

5 Step 5

A mixture of morpholine-4-carboxylic acid (1*R*)-2-trimethylsilanylethyl)amide (1.76 g), *N*-hydroxybenzotriazole (HOBT) (0.910 g, 5.95 mmol), (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (EDCI) (1.370 g, 7.14 mmol), and (R)-2-amino-1-benzoxazol-2-yl-propan-1-ol (1.472 g, 7.14 mmol) in methylene chloride (15 ml) was cooled on ice and treated 10 with *N*-methylmorpholine (0.910 ml, 8.9 mmol). The reaction mixture was stirred at room temperature for 2 h and was then poured into a solution of water (50 ml), 1N HCl (15 ml), brine (50 ml) and ice. The product was extracted with ethyl acetate and the combined organic layers were washed with saturated NaHCO<sub>3</sub> and then brine. The extracts were dried over magnesium sulfate and evaporated to give morpholine-4-carboxylic acid {1(*R*)-[1(*S*)-(benzoxazol-2-ylhydroxymethyl)propylcarbamoyl]-2-trimethylsilanylethyl}amide (2.476 g, 5.36 mmol) as a 15 semi-solid mixture of diastereomers.

Step 6

A solution of morpholine-4-carboxylic acid{1(*R*)-[1(*S*)-(benzoxazol-2-ylhydroxymethyl)propylcarbamoyl]-2-trimethylsilanylethyl}amide (2.476 g) in methylene chloride (33 ml) 20 was cooled on an ice/salt bath to -2° C and treated with sodium bromide (0.612 g, 6 mmol), sodium bicarbonate (0.504 g, 6 mmol), and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (0.06 mmol). A solution of sodium hypochlorite (11 ml, 6%, 9 mmol) (Commercial laundry bleach was used as the oxidant and the quantity was calculated assuming the weight of sodium hypochlorite to be 6.5%) in water (23 ml) was then added dropwise to the reaction mixture with rapid stirring over 25 45 min. while the internal reaction temperature was maintained near 0° C. After the reaction was complete (HPLC), the reaction was quenched by addition of 10% aqueous sodium thiosulfate (10 ml). The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water, then brine and dried over magnesium sulfate. Evaporation of the solvent gave a tan colored foam (1.879 g) which was 30 dissolved in i-propyl acetate (3 ml), diluted with *tert*-butylmethyl ether (8 ml) and cooled in the freezer overnight. Filtration of the solid gave the title compound (1.396 g).

Examples

Biological Examples

Example 1

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10  $\mu$ L of dimethyl 5 sulfoxide (DMSO) and then diluted into assay buffer (40  $\mu$ L, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25  $\mu$ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-FR-AMC (20 10 nMoles in 25  $\mu$ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at ( $\lambda$  460 nm) for 5 minutes. Apparent inhibition constants ( $K_i$ ) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity.

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Example 2

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10  $\mu$ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40  $\mu$ L, comprising: MES, 50 mM (pH 5.5); 20 EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25  $\mu$ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25  $\mu$ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at ( $\lambda$  460 nm) for 5 minutes. Apparent inhibition constants ( $K_i$ ) were 25 calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin K inhibitory activity.

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Example 3

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10  $\mu$ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40  $\mu$ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25  $\mu$ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate,

5 covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (1 nMoles in 25  $\mu$ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at ( $\lambda$  460 nm) for 5 minutes. Apparent inhibition constants ( $K_i$ ) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to

10 exhibit cathepsin L inhibitory activity.

**Example 4**  
**Cathepsin S Assay**

Solutions of test compounds in varying concentrations were prepared in 10  $\mu$ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40  $\mu$ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM);  $\beta$ -mercaptoethanol, 2.5 mM; and BSA, 0.001%. Human cathepsin S (0.05 pMoles in 25  $\mu$ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Val-Val-Arg-AMC (3 nMoles in 25  $\mu$ L of assay buffer containing 10% DMSO) was added to the assay solutions and hydrolysis was followed spectrophotometrically (Ex: 355nm, Em: 460nm) for 5 minutes. Apparent inhibition constants ( $K_i$ ) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin S inhibitory activity.

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**Example 5**  
**Cathepsin F Assay**

Solutions of test compounds in varying concentrations were prepared in 10  $\mu$ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40  $\mu$ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM); DTT, 2.5 mM; and BSA, 0.01%. Human cathepsin F (0.1 pMoles in 25  $\mu$ L of assay buffer) was added to the dilutions. The assay solutions were mixed for

5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-  
Phe-Arg-AMC (2 nMoles in 25  $\mu$ L of assay buffer containing 10% DMSO) was added to the  
assay solutions and hydrolysis was followed spectrophotometrically (at  $\lambda$  460 nm) for 5 minutes.  
Apparent inhibition constants ( $K_i$ ) were calculated from the enzyme progress curves using  
5 standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to  
exhibit cathepsin F inhibitory activity.

#### Example 6

##### 10 *In vitro* Lip10 accumulation assay

During normal antigen presentation, Lip10 is proteolytically degraded to enable loading of  
a peptide fragment and subsequent MHC-II presentation on the surface of antigen presenting cells.  
The cleavage process is mediated by Cathepsin S. Thus, the Lip10 assay is an *in vitro* measure of a  
15 compound's ability to block cathepsin S and by extension antigen presentation. A compound that  
causes the accumulation of Lip10 at low concentration would be expected to block presentation of  
antigens.

Method:

Raji cells ( $4 \times 10^6$ ) were cultured with 0.02% DMSO or different concentrations of  
20 Cathepsin S inhibitors in RPMI medium 1640 containing 10% (v/v) FBS, 10 mM HEPES, 2 mM  
L-glutamine, and 1 mM sodium pyruvate for four hours at 37°C in 5% CO<sub>2</sub> humidified  
atmosphere. After the culture period, cells were washed with cold PBS and cells were then lysed  
in NP-40 lysis buffer (5 mM EDTA, 1% NP-40, 150 mM NaCl, and 50 mM Tris, pH 7.6) with  
protease inhibitors. Protein determinations were performed and lysate samples were boiled in  
25 reducing SDS sample buffer. Proteins were separated by electrophoresis on 12% NuPAGE® Bis-  
Tris gels. Proteins were then transferred to nitrocellulose membranes, and after incubation with  
blocking buffer (5% non-fat dry milk in PBS-Tween), the blots were incubated with the primary  
antibody against human CD74 invariant chain synthetic peptide (1.5 to 2  $\mu$ g/ml of mouse anti-  
CD74 monoclonal antibody, PIN.1, Stressgen Biotechnologies). Blots were then incubated with  
30 the secondary antibody, horseradish peroxidase conjugated donkey anti-mouse IgG, at a 1:10,000  
dilution. Immunoreactive proteins were detected by chemiluminescence reaction using Pierce  
Super Signal® West Pico chemiluminescence substrate.

### Pharmaceutical Composition Examples

The following are representative pharmaceutical formulations containing a compound  
5 of the present invention.

#### Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

	Ingredient	Quantity per tablet, mg
10	compound of this invention	400
	cornstarch	50
	croscarmellose sodium	25
15	lactose	120
	magnesium stearate	5

#### Capsule Formulation

20 The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

	Ingredient	Quantity per capsule, mg
20	compound of this invention	200
	lactose, spray-dried	148
25	magnesium stearate	2

#### Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration.

	Ingredient	Amount
30	compound of this invention	1.0 g
	fumaric acid	0.5 g
	sodium chloride	2.0 g
	methyl paraben	0.15 g
35	propyl paraben	0.05 g
	granulated sugar	25.5 g
	sorbitol (70% solution)	12.85 g
	Veegum K (Vanderbilt Co.)	1.0 g
	flavoring	0.035 ml
40	colorings	0.5 mg
	distilled water	q.s. to 100 ml

#### Injectable Formulation

45 The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	1.2 g

sodium acetate buffer solution,	0.4 M 2.0 ml
HCl (1 N) or NaOH (1 N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 ml

5 All of the above ingredients, except water, are combined and heated to 60-70 °C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

#### Suppository Formulation

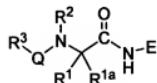
10 A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15	balance

15 The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not  
 20 restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is Claimed:

1. A method for treating a disease in an animal mediated by cysteine proteases which method comprises administering to the animal a therapeutically effective amount of a compound of Formula (I):



(I)

5 where:

Q is -CO-, -SO<sub>2</sub>-, -OCO-, -NR<sup>4</sup>CO-, -NR<sup>4</sup>SO<sub>2</sub>-, or -CHR- where R is haloalkyl and R<sup>4</sup> is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or aralkyl;

E is:

10 (i) -C(R<sup>5</sup>)(R<sup>6</sup>)X<sup>1</sup> where X<sup>1</sup> is -CHO, -C(R<sup>7</sup>)(R<sup>8</sup>)CF<sub>3</sub>, -C(R<sup>7</sup>)(R<sup>8</sup>)CF<sub>2</sub>CF<sub>2</sub>R<sup>9</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)R<sup>10</sup>, -CH=CHS(O)<sub>2</sub>R<sup>10</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)C(R<sup>7</sup>)(R<sup>8</sup>)OR<sup>10</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)CH<sub>2</sub>OR<sup>10</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)C(R<sup>7</sup>)(R<sup>8</sup>)R<sup>10</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)CH<sub>2</sub>N(R<sup>11</sup>)SO<sub>2</sub>R<sup>10</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)CF<sub>2</sub>C(O)NR<sup>10</sup>R<sup>11</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)C(O)NR<sup>10</sup>R<sup>11</sup>, -C(R<sup>7</sup>)(R<sup>8</sup>)C(O)N(R<sup>11</sup>)(CH<sub>2</sub>)<sub>2</sub>OR<sup>11</sup>, or -C(R<sup>7</sup>)(R<sup>8</sup>)C(O)N(R<sup>11</sup>)(CH<sub>2</sub>)<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>; or

15 (ii) -C(R<sup>5a</sup>)(R<sup>6a</sup>)CN;

where:

R<sup>5</sup> and R<sup>5a</sup> are independently hydrogen or alkyl; and

20 R<sup>6</sup> and R<sup>6a</sup> are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, -alkylene-X<sup>2</sup>-R<sup>12</sup> (where X<sup>2</sup> is -O-, -NR<sup>13</sup>-, -S(O)<sub>n1</sub>-, -CONR<sup>13</sup>-, -NR<sup>13</sup>CO-, -NR<sup>13</sup>C(O)O-, -NR<sup>13</sup>CONR<sup>13</sup>-, -OCOCONR<sup>13</sup>-, -NR<sup>13</sup>SO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>13</sup>-, -NR<sup>13</sup>SO<sub>2</sub>NR<sup>13</sup>-, -CO-, or -OCO- where n1 is 0-2 and each R<sup>13</sup> is hydrogen or alkyl) and R<sup>12</sup> hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl wherein the aromatic or alicyclic ring in R<sup>6</sup> and R<sup>6a</sup> is optionally substituted with one, two, or three R<sup>8</sup> independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, nitro, aryloxy, benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl where the aromatic or alicyclic ring in R<sup>8</sup> is optionally substituted with one or two substituents independently selected from alkyl, halo,

alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl; or

R<sup>5</sup> and R<sup>6</sup> and R<sup>5a</sup> and R<sup>6a</sup> taken together with the carbon atom to which both R<sup>5</sup> and R<sup>6</sup> and R<sup>5a</sup> and R<sup>6a</sup> are attached form (i) cycloalkylene optionally substituted with one or two R<sup>b</sup>

5 independently selected from alkyl, halo, alkylamino, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxycarbonyl, or (ii) heterocycloalkylene optionally substituted with one to four alkyl or one or two R<sup>c</sup> independently selected from alkyl, haloalkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -S(O)<sub>n2</sub>R<sup>14</sup>, -alkylene-S(O)<sub>n2</sub>R<sup>15</sup>, -COOR<sup>16</sup>, -alkylene-COOR<sup>17</sup>, -CONHR<sup>18</sup>R<sup>19</sup>, or -alkylene-CONHR<sup>20</sup>R<sup>21</sup> (where n2 is 0-2 and R<sup>14</sup>-R<sup>17</sup>, R<sup>18</sup> and R<sup>20</sup> are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and R<sup>19</sup> and R<sup>21</sup> are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to cycloalkylene

10 or heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, or acyl;

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R<sup>7</sup> is hydrogen or alkyl;

R<sup>8</sup> is hydroxy; or

20 R<sup>7</sup> and R<sup>8</sup> together form oxo;

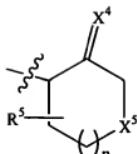
R<sup>9</sup> is hydrogen, halo, alkyl, aralkyl or heteroaralkyl;

R<sup>10</sup> is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in R<sup>10</sup> is optionally substituted with one, two, or three R<sup>d</sup> independently selected from alkyl, haloalkyl,

25 alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryl, aralkyl, heteroaryl, amino, monosubstituted amino, disubstituted amino, carbamoyl, or acyl wherein the aromatic or alicyclic ring in R<sup>d</sup> is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino; and

R<sup>11</sup> is hydrogen or alkyl; or

(iii) a group of formula (a):



(a)

where:

5 n is 0, 1, or 2;  
 $X^4$  is selected from  $-\text{NR}^{22}-$ ,  $-\text{S}-$ , or  $-\text{O}-$  where  $\text{R}^{22}$  is hydrogen, alkyl, or alkoxy; and  
 $X^5$  is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{SO}_2-$ , or  $-\text{NR}^{23}-$  where  $\text{R}^{23}$  is selected from hydrogen, alkyl, haloalkyl,  
hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl,  
heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,  $-\text{S}(\text{O})_2\text{R}^{24}$ ,  $-\text{alkylene-S(O)}_{n3}\text{R}^{25}$ ,  $-\text{COOR}^{26}$ ,  $-\text{alkylene-COOR}^{27}$ ,  $-\text{CONR}^{28}\text{R}^{29}$ , or  $-\text{alkylene-CONR}^{30}\text{R}^{31}$  (where  $n3$  is 0-2 and  $\text{R}^{24}$ - $\text{R}^{27}$ ,  $\text{R}^{28}$  and  
10  $\text{R}^{30}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,  
cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl and  $\text{R}^{29}$  and  $\text{R}^{31}$  are  
independently hydrogen or alkyl) where the aromatic or alicyclic ring in  $\text{R}^{23}$  is optionally  
substituted with one, two, or three substituents independently selected from alkyl, haloalkyl,  
15 alkoxy, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl  
and one substituent selected from aryl, aralkyl, heteroaryl, or heteroaralkyl; and  
 $\text{R}^5$  is as defined above;  
 $\text{R}^1$  is hydrogen or alkyl;  
20  $\text{R}^{1a}$  is 1,1-dialkylsilylan-4-ylalkylene or  $-(\text{alkylene})\text{-SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  is alkyl,  $\text{R}^{33}$  is  
alkyl, and  $\text{R}^{34}$  is alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, or  
heterocycloalkylalkyl or  $\text{R}^{33}$  and  $\text{R}^{34}$  together with Si form a heterocycloalkylene ring containing a  
25 Si atom and 3 to 7 carbon ring atoms wherein one or two carbon ring atoms are optionally  
independently replaced with  $-\text{NH}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{SO}_2-$ ,  $-\text{CO}-$ ,  $-\text{CONH}-$ , or  $-\text{SO}_2\text{NH}-$  and  
wherein the aralkyl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylene ring in  $\text{R}^{1a}$  is  
optionally substituted on the ring with one, two, or three  $\text{R}^e$  independently selected from alkyl,  
30 haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted  
amino, disubstituted amino, nitro, aryloxy, benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl and  
further wherein the aromatic or alicyclic ring in  $\text{R}^e$  is optionally substituted with one or two

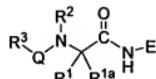
substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl;

R<sup>2</sup> is hydrogen or alkyl;

R<sup>3</sup> is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,

5 heterocycloalkyl, heterocycloalkylalkyl, or -alkylene-X<sup>6</sup>-R<sup>35</sup> [wherein X<sup>6</sup> is -NR<sup>36</sup>-, -O-, -S(O)<sub>n4</sub>-, -CO-, -COO-, -OCO-, -NR<sup>36</sup>CO-, -CONR<sup>36</sup>-, -NR<sup>36</sup>SO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>36</sup>-, -NR<sup>36</sup>COO-, -OCONR<sup>36</sup>-, -NR<sup>36</sup>CONR<sup>37</sup>-, or -NR<sup>36</sup>SO<sub>2</sub>NR<sup>37</sup>- (where each R<sup>36</sup> and R<sup>37</sup> are independently hydrogen, alkyl, or acyl and n4 is 0-2) and R<sup>35</sup> is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the 10 alkylene chain in R<sup>3</sup> is optionally substituted with one to four halo atoms and the aromatic and alicyclic rings in R<sup>3</sup> are optionally substituted by one, two, or three R<sup>f</sup> independently selected from alkyl, aminoalkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryloxy, benzyloxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, 15 alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, aralkylaminosulfonyl, aminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, amino, monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in R<sup>f</sup> 20 are optionally substituted with one, two, or three R<sup>g</sup> wherein R<sup>g</sup> is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl; or a pharmaceutically acceptable salts thereof.

25 2. A compound of Formula (I):



(I)

wherein:

Q is -CO-, -SO<sub>2</sub>-, -OCO-, -NR<sup>4</sup>CO-, -NR<sup>4</sup>SO<sub>2</sub>-, or -CHR- where R is haloalkyl and R<sup>4</sup> is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or aralkyl;

E is:

(i)  $-\text{C}(\text{R}^5)(\text{R}^6)\text{X}^1$  where  $\text{X}^1$  is  $-\text{C}(\text{R}^7)(\text{R}^8)\text{R}^{10}$ ,  $-\text{CH}=\text{CHS}(\text{O})_2\text{R}^{10}$ ,  
 $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{R}^7)(\text{R}^8)\text{OR}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CH}_2\text{OR}^{10}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{CH}_2\text{N}(\text{R}^{11})\text{SO}_2\text{R}^{10}$ ,  
 $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^{11})(\text{CH}_2)_2\text{OR}^{11}$ ,  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$  or  
5  $-\text{C}(\text{R}^7)(\text{R}^8)\text{C}(\text{O})\text{N}(\text{R}^{11})(\text{CH}_2)_2\text{NR}^{10}\text{R}^{11}$ ; or  
(ii)  $-\text{C}(\text{R}^{5a})(\text{R}^{6a})\text{CN}$ ;

where:

10  $\text{R}^5$  and  $\text{R}^{5a}$  are independently hydrogen or alkyl; and  
 $\text{R}^6$  and  $\text{R}^{6a}$  are independently selected from the group consisting of hydrogen, alkyl,  
haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl,  
heterocycloalkylalkyl, -alkylene- $\text{X}^2-\text{R}^{12}$  (where  $\text{X}^2$  is  $-\text{O}-$ ,  $-\text{NR}^{13}-$ ,  $-\text{S}(\text{O})_{n1}-$ ,  $-\text{CONR}^{13}-$ ,  $-\text{NR}^{13}\text{CO}-$ ,  
 $-\text{NR}^{13}\text{C}(\text{O})\text{O}-$ ,  $-\text{NR}^{13}\text{CONR}^{13}-$ ,  $-\text{OCONR}^{13}-$ ,  $-\text{NR}^{13}\text{SO}_2-$ ,  $-\text{SO}_2\text{NR}^{13}-$ ,  $-\text{NR}^{13}\text{SO}_2\text{NR}^{13}-$ ,  $-\text{CO}-$ , or  $-\text{OCO}-$  where  $n1$  is 0-2 and each  $\text{R}^{13}$  is hydrogen or alkyl) and  $\text{R}^{12}$  hydrogen, alkyl, haloalkyl,  
cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or  
15 heteroaralkyl wherein the aromatic or alicyclic ring in  $\text{R}^6$  and  $\text{R}^{6a}$  is optionally substituted with  
one, two, or three  $\text{R}^8$  independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy,  
halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, nitro, aryloxy,  
benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl where the aromatic or alicyclic ring in  $\text{R}^8$  is  
optionally substituted with one or two substituents independently selected from alkyl, halo,  
20 alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or  
alkoxycarbonyl; or  
25  $\text{R}^5$  and  $\text{R}^6$  and  $\text{R}^{6a}$  taken together with the carbon atom to which both  $\text{R}^5$  and  $\text{R}^6$   
and  $\text{R}^{5a}$  and  $\text{R}^{6a}$  are attached form (i) cycloalkylene optionally substituted with one or two  $\text{R}^b$   
independently selected from alkyl, halo, alkylamino, dialkylamino, aryl, aralkyl, cycloalkyl,  
cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxy carbonyl, or (ii)  
30 heterocycloalkylene optionally substituted with one to four alkyl or one or two  $\text{R}^c$  independently  
selected from alkyl, haloalkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl,  
aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl,  
heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl,  $-\text{S}(\text{O})_{n2}\text{R}^{14}$ , -alkylene- $\text{S}(\text{O})_{n2}-$   
 $\text{R}^{15}$ ,  $-\text{COOR}^{16}$ , -alkylene- $\text{COOR}^{17}$ ,  $-\text{CONHR}^{18}\text{R}^{19}$ , or -alkylene- $\text{CONHR}^{20}\text{R}^{21}$  (where  $n2$  is 0-2 and  
 $\text{R}^{14}-\text{R}^{17}$ ,  $\text{R}^{18}$  and  $\text{R}^{20}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl,  
heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and  $\text{R}^{19}$  and  $\text{R}^{21}$  are independently

hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to cycloalkylene or heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, or acyl;

5        R<sup>7</sup> is hydrogen or alkyl;

R<sup>8</sup> is hydroxy; or

R<sup>7</sup> and R<sup>8</sup> together form oxo;

R<sup>10</sup> is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,

heterocycloalkyl, or heterocycloalkylalkyl wherein the aromatic or alicyclic ring in R<sup>10</sup> is

10      optionally substituted with one, two, or three R<sup>4</sup> independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryl, aralkyl, heteroaryl, amino, monosubstituted amino, disubstituted amino, carbamoyl, or acyl wherein the aromatic or alicyclic ring in R<sup>4</sup> is optionally substituted with one, two, or three substituents independently selected

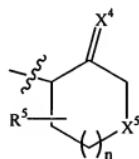
15      from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, amino, alkylamino, or dialkylamino; and

R<sup>11</sup> is hydrogen or alkyl provided that when E is -C(R<sup>7</sup>)(R<sup>8</sup>)C(O)NR<sup>10</sup>R<sup>11</sup> then R<sup>11</sup> is alkyl;

or

(iii)    a group of formula (a):

20



(a)

where:

n is 0, 1, or 2;

25      X<sup>4</sup> is selected from -NR<sup>22</sup>-, -S-, or -O- where R<sup>22</sup> is hydrogen, alkyl, or alkoxy; and

X<sup>5</sup> is -O-, -S-, -SO<sub>2</sub>-, or -NR<sup>23</sup>- where R<sup>23</sup> is selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, -S(O)<sub>2</sub>R<sup>24</sup>, -alkylene-S(O)<sub>n3</sub>R<sup>25</sup>, -COOR<sup>26</sup>, -

alkylene-COOR<sup>27</sup>, -CONR<sup>28</sup>R<sup>29</sup>, or -alkylene-CONR<sup>30</sup>R<sup>31</sup> (where n3 is 0-2 and R<sup>24</sup>-R<sup>27</sup>, R<sup>28</sup> and R<sup>30</sup> are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl and R<sup>29</sup> and R<sup>31</sup> are independently hydrogen or alkyl) where the aromatic or alicyclic ring in R<sup>23</sup> is optionally

5 substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl and one substituent selected from aryl, aralkyl, heteroaryl, or heteroaralkyl; and

R<sup>5</sup> is as defined above;

R<sup>1</sup> is hydrogen or alkyl;

10 R<sup>1a</sup> is 1,1-dialkylsilinan-4-ylalkylene or -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl, R<sup>33</sup> is alkyl, and R<sup>34</sup> is alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, or heterocycloalkylalkyl or R<sup>33</sup> and R<sup>34</sup> together with Si form a heterocycloalkylene ring containing a Si atom and 3 to 7 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with -NH-, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CONH-, or -SO<sub>2</sub>NH- and

15 wherein the aralkyl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylene ring in R<sup>1a</sup> is optionally substituted on the ring with one, two, or three R<sup>6</sup> independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, nitro, aryloxy, benzyloxy, acyl, alkylsulfonyl, or arylsulfonyl and further wherein the aromatic or alicyclic ring in R<sup>6</sup> is optionally substituted with one or two

20 substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl;

R<sup>2</sup> is hydrogen or alkyl;

R<sup>3</sup> is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, or -alkylene-X<sup>6</sup>-R<sup>35</sup> [wherein X<sup>6</sup> is -NR<sup>36</sup>-, -O-, -S(O)n4-, -CO-, -COO-, -OCO-, -NR<sup>36</sup>CO-, -CONR<sup>36</sup>-, -NR<sup>36</sup>SO<sub>2</sub>-, -SO<sub>2</sub>NR<sup>36</sup>-, -NR<sup>36</sup>COO-, -OCONR<sup>36</sup>-, -NR<sup>36</sup>CONR<sup>37</sup>-, or -NR<sup>36</sup>SO<sub>2</sub>NR<sup>37</sup>- (where each R<sup>36</sup> and R<sup>37</sup> are independently hydrogen, alkyl, or acyl and n4 is 0-2) and R<sup>35</sup> is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the alkylene chain in R<sup>3</sup> is optionally substituted with one to four halo atoms and the aromatic and

30 alicyclic rings in R<sup>3</sup> are optionally substituted by one, two, or three R<sup>f</sup> independently selected from alkyl, aminoalkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl,

heterocycloalkylalkyl, aryloxy, benzyloxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, 5 aralkylaminosulfonyl, aminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, amino, monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in  $R^f$  are optionally substituted with one, two, or three  $R^g$  wherein  $R^g$  is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, monosubstituted amino, dialkylamino, aryl, 10 heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl; or a pharmaceutically acceptable salts thereof.

3. The method of Claim 1 wherein:

E is  $-C(R^5)(R^6)X^1$  in which:

$R^5$  is hydrogen;

15  $R^6$  is alkyl; and

$X^1$  is  $-CHO$ ,  $-C(O)R^{10}$ ,  $-C(O)CF_3$ ,  $-C(O)CF_2CF_2R^9$ ,  $-CH=CHS(O)R^{10}$ ,

$-C(O)CF_2C(O)NR^{10}R^{11}$ ,  $-C(O)C(O)NR^{10}R^{11}$ ,  $-C(O)CH_2OR^{10}$ ,  $-C(O)CH_2N(R^{11})SO_2R^{10}$ ,

$-C(O)C(O)N(R^{11})(CH_2)OR^{11}$ ,  $-C(O)C(O)N(R^{11})(CH_2)_2NHR^{11}$  or  $-C(O)C(O)R^{10}$  wherein  $R^{10}$  is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl wherein the aromatic ring is optionally substituted with  $R^d$  selected from heteroaryl, aryl, alkyl, or alkoxyalkyl

20  $R^{11}$  is hydrogen or alkyl and  $R^9$  is halo.

4. The method of Claim 1 wherein E is  $-CHR^6C(O)R^{10}$  where  $R^6$  is alkyl and  $R^{10}$  is heteroaryl optionally substituted with one or two  $R^d$  independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, aryl,

25 heteroaryl, amino, monosubstituted amino, disubstituted amino, or acyl wherein the aromatic or alicyclic ring in  $R^d$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, or dialkylamino.

30 5. The method of Claim 1 wherein wherein E is  $-CR^{5a}R^{6a}CN$  wherein  $R^{5a}$  and  $R^{6a}$  together with the carbon atom to which they are attached form cycloalkylene optionally substituted with one or two  $R^b$  independently selected from alkyl, halo, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxycarbonyl, or aryloxycarbonyl.

6. The method of Claim 1 wherein E is  $-\text{CR}^{5a}\text{R}^{6a}\text{CN}$  wherein  $\text{R}^{5a}$  and  $\text{R}^{6a}$  together with the carbon atom to which they are attached form heterocycloalkylene optionally substituted with one to four alkyl or one or two  $\text{R}^c$  which are independently selected from alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl,  $-\text{S}(\text{O})_{n2}\text{R}^{14}$ , -alkylene- $\text{S}(\text{O})_{n2}\text{R}^{15}$ , - $\text{COOR}^{16}$ , -alkylene- $\text{COOR}^{17}$ , - $\text{CONR}^{18}\text{R}^{19}$ , or -alkylene- $\text{CONR}^{20}\text{R}^{21}$  (where  $n2$  is 0-2 and  $\text{R}^{14}$ - $\text{R}^{17}$ ,  $\text{R}^{18}$  and  $\text{R}^{20}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocycloalkyl and  $\text{R}^{19}$  and  $\text{R}^{21}$  are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monosubstituted amino, disubstituted amino, or acyl.

7. The method of Claim 1 wherein E is  $-\text{CR}^{5a}\text{R}^{6a}\text{CN}$  wherein  $\text{R}^{5a}$  and  $\text{R}^{6a}$  together with the carbon atom to which they are attached form piperidin-4-yl substituted at the 1-position with ethyl, *n*- or 2-propyl, tetrahydrothiopyran-4-yl tetrahydrothiopyran-4-yl-1-oxide, or tetrahydrothiopyran-4-yl-1,1-dioxide.

8. The method of any one of the Claims 1-7 wherein  $\text{R}^1$  and  $\text{R}^2$  are hydrogen and Q is  $-\text{CO}-$ .

9. The method of any one of the Claims 1-7 wherein  $\text{R}^1$  and  $\text{R}^2$  are hydrogen and Q is  $-\text{CH}(\text{CF}_3)-$ .

10. The method of any one of the Claims 1-9 wherein  $\text{R}^{1a}$  is  $-(\text{alkylene})\text{-SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  is alkyl,  $\text{R}^{33}$  is alkyl, and  $\text{R}^{34}$  is alkyl.

11. The method of any one of the Claims 1-9 wherein  $\text{R}^{1a}$  is a group having the structure:

12. The method of any one of the Claims 1-9 wherein  $\text{R}^{1a}$  is  $-(\text{alkylene})\text{-SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  is alkyl and  $\text{R}^{33}$  and  $\text{R}^{34}$  together with Si form a heterocycloalkylene ring containing a Si atom and 4 or 5 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with  $-\text{NH-}$ ,  $-\text{O-}$ ,  $-\text{S-}$ ,  $-\text{SO-}$ ,  $-\text{SO}_2-$ ,  $-\text{CO-}$ ,  $-\text{CONH-}$ , or  $-\text{SO}_2\text{NH-}$ .

13. The method of any one of the Claims 1-8 wherein  $\text{R}^{1a}$  is  $-(\text{alkylene})\text{-SiR}^{32}\text{R}^{33}\text{R}^{34}$  where  $\text{R}^{32}$  and  $\text{R}^{33}$  are alkyl and  $\text{R}^{34}$  is cycloalkylalkyl.

14. The method of any one of the Claims 1-8 wherein R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> and R<sup>33</sup> are alkyl and R<sup>34</sup> is aralkyl.

15. The method of any one of the Claims 1-14 wherein R<sup>3</sup> is heterocycloalkyl, aryl, or heteroaryl optionally substituted with one or two R<sup>f</sup>.

5 16. The compound of Claim 2 wherein:

E is -C(R<sup>5</sup>)(R<sup>6</sup>)X<sup>1</sup> in which:

R<sup>5</sup> is hydrogen;

R<sup>6</sup> is alkyl; and

X<sup>1</sup> is -C(O)R<sup>10</sup>, -CH=CHS(O)<sub>2</sub>R<sup>10</sup>, -C(O)C(O)NR<sup>10</sup>R<sup>11</sup>, -C(O)CH<sub>2</sub>OR<sup>10</sup>,

10 -C(O)CH<sub>2</sub>N(R<sup>11</sup>)SO<sub>2</sub>R<sup>10</sup>, -C(O)C(O)N(R<sup>11</sup>)(CH<sub>2</sub>)<sub>2</sub>OR<sup>11</sup>, or -C(O)C(O)N(R<sup>11</sup>)(CH<sub>2</sub>)<sub>2</sub>NHR<sup>11</sup> wherein R<sup>10</sup> is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl wherein the aromatic ring is optionally substituted with R<sup>d</sup> selected from heteroaryl, aryl, alkyl, or alkoxyalkyl and R<sup>11</sup> is hydrogen or alkyl.

17. The compound of Claim 2 wherein E is -CHR<sup>6</sup>C(O)R<sup>10</sup> where R<sup>6</sup> is alkyl and R<sup>10</sup> is heteroaryl optionally substituted with one or two R<sup>d</sup> independently selected from alkyl, haloalkyl, alkoxy, alkoxyalkyl, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, aryl, heteroaryl, amino, monosubstituted amino, disubstituted amino, or acyl wherein the aromatic or alicyclic ring in R<sup>d</sup> is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxy carbonyl, 20 amino, alkylamino, or dialkylamino.

18. The compound of Claim 2 wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cycloalkylene optionally substituted with one or two R<sup>b</sup> independently selected from alkyl, halo, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxy carbonyl.

25 19. The compound of Claim 2 wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form heterocycloalkylene optionally substituted with one to four alkyl or one or two R<sup>c</sup> which are independently selected from alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -S(O)<sub>n2</sub>R<sup>14</sup>, -alkylene-S(O)<sub>n2</sub>R<sup>15</sup>, -COOR<sup>16</sup>, -alkylene-COOR<sup>17</sup>, -CONR<sup>18</sup>R<sup>19</sup>, or -alkylene-CONR<sup>20</sup>R<sup>21</sup> (where n2 is 0-2 and R<sup>14</sup>-R<sup>17</sup>, R<sup>18</sup> and R<sup>20</sup> are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or

heterocycloalkyl and R<sup>19</sup> and R<sup>21</sup> are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, benzyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monosubstituted 5 amino, disubstituted amino, or acyl.

20. The compound of Claim 2 wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form piperidin-4-yl substituted at the 1-position with ethyl, n- or 2-propyl, tetrahydrothiopyran-4-yl tetrahydrothiopyran-4-yl-1-oxide, or tetrahydrothiopyran-4-yl-1,1-dioxide.

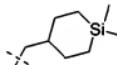
10 21. The compound of any one of the Claims 2 and 16-20 wherein R<sup>1</sup> and R<sup>2</sup> are hydrogen and Q is -CO-.

22. The compound of any one of the Claims 2 and 16-20 wherein R<sup>1</sup> and R<sup>2</sup> are hydrogen and Q is -CH(CF<sub>3</sub>)-.

23. The compound of any one of the Claims 2 and 16-21 wherein R<sup>1a</sup> is -(alkylene)-

15 SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl, R<sup>33</sup> is alkyl, and R<sup>34</sup> is alkyl.

24. The compound of any one of the Claims 2 and 16-21 wherein R<sup>1a</sup> is a group having the structure:



25. The compound of any one of the Claims 2 and 16-21 wherein R<sup>1a</sup> is -(alkylene)-

20 SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl and R<sup>33</sup> and R<sup>34</sup> together with Si form a heterocycloalkylene ring containing a Si atom and 4 or 5 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with -NH-, -O-, -S-, -SO-, -SO<sub>2</sub>-, -CO-, -CONH-, or -SO<sub>2</sub>NH-.

26. The compound of any one of the Claims 2 and 16-21 wherein R<sup>1a</sup> is -(alkylene)-

25 SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> and R<sup>33</sup> are alkyl and R<sup>34</sup> is cycloalkylalkyl.

27. The compound of any one of the Claims 2 and 16-21 wherein R<sup>1a</sup> is -(alkylene)-

SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> and R<sup>33</sup> are alkyl and R<sup>34</sup> is aralkyl.

28. The compound of any one of the Claims 2 and 16-27 wherein R<sup>3</sup> is heterocycloalkyl, aryl, or heteroaryl optionally substituted with one or two R<sup>1</sup>.

29. The compound of Claim 2 wherein R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl, R<sup>33</sup> is alkyl, and R<sup>34</sup> is alkyl.

30. The compound of Claim 2 wherein R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> is alkyl and R<sup>33</sup> and R<sup>34</sup> together with Si form a heterocycloalkylene ring containing a Si atom and 4 or 5

5 carbon ring atoms wherein one or two carbon ring atoms are optionally independently replaced with -NH-, -O-, -S-, -SO<sub>2</sub>-, -CO-, -CONH-, or -SO<sub>2</sub>NH-.

31. The compound of Claim 2 wherein R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> and R<sup>33</sup> are alkyl and R<sup>34</sup> is cycloalkylalkyl.

32. The compound of Claim 2 wherein R<sup>1a</sup> is -(alkylene)-SiR<sup>32</sup>R<sup>33</sup>R<sup>34</sup> where R<sup>32</sup> and R<sup>33</sup> are alkyl and R<sup>34</sup> is aralkyl.

10 33. The compound of any one of the Claims 29-32 wherein Q is -CO-; and R<sup>1</sup> and R<sup>2</sup> are hydrogen.

34. The compound of any one of the Claims 29-33 wherein E is -CHR<sup>6</sup>C(O)R<sup>10</sup> where R<sup>6</sup> is ethyl, propyl, or butyl and R<sup>10</sup> is benzoxazol-2-yl, 4-azabenzoxazol-2-yl, 2-pyridin-3-yl-[1,3,4]-

15 oxadiazol-5-yl, 2-pyridin-4-yl-[1,3,4]-oxadiazol-5-yl, 2-ethyl-[1,3,4]-oxadiazol-5-yl, 2-isopropyl-[1,3,4]-oxadiazol-5-yl, 2-*tert*-butyl-[1,3,4]-oxadiazol-5-yl, 2-phenyl-[1,3,4]-oxadiazol-5-yl, 2-methoxymethyl-[1,3,4]-oxadiazol-5-yl, 2-furan-2-yl-[1,3,4]-oxadiazol-5-yl, 2-thien-2-yl-[1,3,4]-

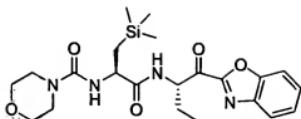
20 oxadiazol-5-yl, 2-(4-methoxy-phenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-methoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(3-methoxy-phenyl)-[1,3,4]-oxadiazol-5-yl, 2-(2-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(3-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-trifluoromethoxyphenyl)-[1,3,4]-oxadiazol-5-yl, 2-(4-dimethylaminophenyl)-[1,3,4]-oxadiazol-5-yl, pyradizin-3-yl, pyrimidin-2-yl, 3-phenyl-[1,2,4]-oxadiazol-5-yl, 3-ethyl-[1,2,4]-oxadiazol-5-yl, 3-cyclopropyl-[1,2,4]-oxadiazol-5-yl, 3-thien-3-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-4-yl-[1,2,4]-oxadiazol-5-yl, 3-pyridin-2-yl-[1,2,4]-oxadiazol-5-yl, 5-ethyl-[1,2,4]-oxadiazol-3-yl, 5-phenyl-[1,2,4]-oxadiazol-3-yl, 5-thien-3-yl-[1,2,4]-oxadiazol-3-yl, 5-trifluoromethyl-[1,2,4]-oxadiazol-3-yl, 5-pyridin-4-yl-[1,2,4]-oxadiazol-3-yl, or 5-phenyloxazol-2-yl.

25 35. The compound of any one of the Claims 29-33 wherein E is -CR<sup>5a</sup>R<sup>6a</sup>CN wherein R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cyclopropylene, piperidin-4-yl substituted at the 1-position with ethyl, *n*- or 2-propyl, tetrahydrothiopyran-4-yl

30 tetrahydrothiopyran-4-yl-1-oxide, or tetrahydrothiopyran-4-yl-1,1-dioxide.

36. The compound of any one of the Claims 29-33 wherein R<sup>3</sup> is tetrahydropyran-4-yl, morpholin-4-yl, pyridin-4-yl, or phenyl.

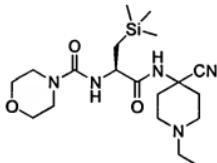
37. A compound having the structure:



namely, {1(*S*)-[1(*S*)-(benzooxazol-2-ylcarbonyl)-propylcarbamoyl]-2-(trimethylsilyl)ethyl}-

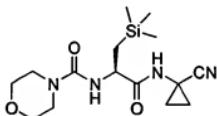
5 amide.

38. A compound having the structure:



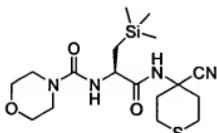
namely, (1*R*)-morpholine-4-carboxylic acid [1-(4-cyano-1-ethylpiperidin-4-ylcarbamoyl)-2-(trimethylsilyl)ethyl]amide.

10 39. A compound having the structure:



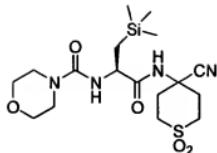
namely, (1*R*)-morpholine-4-carboxylic acid [1-(1-cyanocyclopropylcarbamoyl)-2-(trimethylsilanyl)ethyl]amide.

40. A compound having the structure:



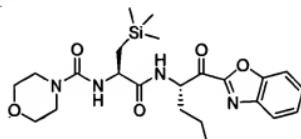
namely, (1*R*)-morpholine-4-carboxylic acid [1-(4-cyanotetrahydrothiopyran-4-ylcarbamoyl)-2-(trimethyl-silanyl)ethyl]amide.

15 41. A compound having the structure:



namely, (1*R*)-morpholine-4-carboxylic acid [1-(4-cyano-1,1-dioxohexahydro-1 $\lambda^6$ -thiopyran-4-ylcarbamoyl)-2-(trimethylsilyl)ethyl]amide.

42. A compound having the structure:



5

namely, {1(*R*)-[1(*S*)-(benzoxazol-2-ylcarbonyl)-butylcarbamoyl]-2-(trimethylsilyl)ethyl}amide.

43. A pharmaceutical composition comprising a compound of any of the Claims 1, 2, and 16-42 and a pharmaceutically acceptable excipient.

44. A method of treating a disease in a patient mediated by Cathepsin S comprising

10 administering to the patient a pharmaceutical composition comprising a compound of any of the Claims 2, 16-42 and a pharmaceutically acceptable excipient.

45. A method of treating a patient undergoing a therapy wherein the therapy causes an immune response in the patient comprising administering to the patient a pharmaceutical composition comprising a compound of any of the Claims 2, 16-43 and a pharmaceutically acceptable

15 excipient.

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## ABSTRACT

The present invention is directed to compounds that are inhibitors of cysteine proteases, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is directed to pharmaceutical compositions comprising these compounds and processes for preparing them. The present invention is also directed to the use of these inhibitors in combination with a therapy that causes a deleterious immune response in patients receiving the therapy.